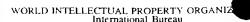
# **PCT**

(51) I a - dissal Datast Classification 7







# INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51)	1) International Fatent Classification 7.							
	C12N 15/12, C07K 14/47, C12N 9/12,							
	5/10, C07K 16/18, A61K 38/17							

**A2** 

### (11) International Publication Number:

WO 00/06728

(43) International Publication Date:

10 February 2000 (10.02.00)

(21) International Application Number:	PCT/US99/17132
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(22) International Filing Date: 28 July 1999 (28.07.99)

# (30) Priority Data:

28 July 1998 (28 07.98)	US
28 July 1998 (28 07.98)	US
14 September 1998 (14.09.98)	US
14 September 1998 (14.09.98)	US
14 October 1998 (14.10.98)	US
14 October 1998 (14.10.98)	US
3 November 1998 (03.11.98)	US
19 November 1998 (19.11.98)	US
22 December 1998 (22.12.98)	US
12 January 1999 (12,01,99)	US
12 January 1999 (12.01.99)	US
	28 July 1998 (28 07.98) 14 September 1998 (14.09.98) 14 September 1998 (14.09.98) 14 October 1998 (14.10.98) 14 October 1998 (14.10.98) 3 November 1998 (03.11.98) 19 November 1998 (19.11.98) 22 December 1998 (22.12.98) 12 January 1999 (12.01.99)

# (63) Related by Continuation (CON) or Continuation-in-Part (CIP) to Earlier Applications

US	Not furnished (CIP)
F:led on	28 July 1998 (28.07.98)
US	09/123,494 (CIP)
Filed on	28 July 1998 (28.07.98)
US	09/152,814 (CIP)
Filed on	14 September 1998 (14.09.98)
US	Not furnished (CIP)
Filed on	14 September 1998 (14.09.98)
US	09/173,482 (CIP)
Filed on	14 October 1998 (14.10.98)
US	Not furnished (CIP)
Filed on	14 October 1998 (14.10.98)
US	60/106,889 (CIP)
Filed on	3 November 1998 (03.11.98)
US	60/109,093 (CIP)
Filed on	19 November 1998 (19.11.98)
US	60/113,796 (CIP)
Filed on	22 December 1998 (22,12,98)
US	09/229,005 (CIP)
Filed on	12 January 1999 (12.01.99)
US	Not furnished (CIP)
Filed on	12 January 1999 (12.01.99)

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(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

## Published

Without international search report and to be republished upon receipt of that report.

### (54) Title: PHOSPHORYLATION EFFECTORS

#### (57) Abstract

The invention provides human phosphorylation effectors (PHSP) and polynucleotides which identify and encode PHSP. The invention also provides expression vectors, host cells, antibodies, agonists, and antagonists. The invention also provides methods for diagnosing, treating, or preventing disorders associated with expression of PHSP.

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# PHOSPHORYLATION EFFECTORS

## **TECHNICAL FIELD**

This invention relates to nucleic acid and amino acid sequences of phosphorylation effectors and to the use of these sequences in the diagnosis, treatment, and prevention of cell proliferative, immune, and neuronal disorders.

Kinases and phosphatases are critical components of intracellular signal transduction mechanisms. Kinases catalyze the transfer of high energy phosphate groups from adenosine triphosphate (ATP) to various target proteins. Phosphatases, in contrast, remove phosphate groups from proteins. Reversible protein phosphorylation is the main strategy for regulating protein activity in eukaryotic cells. In general, proteins are activated by phosphorylation in response to extracellular signals such as hormones, neurotransmitters, and growth and differentiation factors. 15 Protein dephosphorylation occurs when down-regulation of a signaling pathway is required. The coordinate activities of kinases and phosphatases regulate key cellular processes such as proliferation, differentiation, and cell cycle progression. Kinases comprise the largest known enzyme superfamily and are widely varied in their substrate specificities. Kinases may be categorized based on the specific amino acid residues that are phosphorylated in their substrates: protein tyrosine kinases (PTK) phosphorylate tyrosine residues, and protein serine/threonine kinases (STK) phosphorylate serine and/or threonine residues. Almost all kinases contain a conserved 250-300 amino acid catalytic domain. This domain can be further divided into 11 subdomains. N-terminal subdomains I-IV fold into a two-lobed structure which binds and orients the ATP donor molecule, and subdomain V spans the two lobes. C-terminal subdomains VIA-XI 25 bind the protein substrate and transfer the gamma phosphate from ATP to the hydroxyl group of a serine, threonine, or tyrosine residue. Each of the 11 subdomains contains specific catalytic residues or amino acid motifs characteristic of that subdomain. For example, subdomain I contains an 8-amino acid glycine-rich ATP binding consensus motif, subdomain II contains a critical lysine residue required for maximal catalytic activity, and subdomains VI and IX comprise 30 the highly conserved catalytic core. Kinases may also be categorized by additional amino acid sequences, generally between 5 and 100 residues, which either flank or occur within the kinase domain. These additional amino acid sequences regulate kinase activity and determine substrate specificity. (Reviewed in Hardie, G. and Hanks, S. (1995) The Protein Kinase Facts Books, Vol I:7-20 Academic Press, San Diego, CA.)

STKs include both protein kinase A (PKA) and calcium-dependent protein kinase C

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(PKC), both of which transduce signals from plasma membrane receptors. The activities of PKA and PKC are directly regulated by second messenger signaling molecules such as cyclic AMP and diacylglycerol, respectively. A novel kinase identified by genetic analysis in the fission yeast Schizosaccharomyces pombe is encoded by the cek1\* gene and is related to both PKA and PKC 5 (Samejima, I. and Yanagida, M. (1994) Mol. Cell. Biol. 14:6361-6371). cek1+ encodes an unusually large kinase of 1309 amino acids. The kinase domain spans residues 585 to 987, and 112 additional amino acids are present in this domain between subdomains VII and VIII. Overexpression of  $cek1^+$  suppresses mutations in  $cut8^+$ , a gene required for chromosome segregation during mitosis. Therefore, cek1\* may encode a unique member of the PKA/PKC protein family with a role in mitotic signaling and cell cycle progression.

PTKs may be classified as either transmembrane or nontransmembrane proteins. Transmembrane tyrosine kinases function as receptors for most growth factors. Binding of growth factor to the receptor activates the transfer of a phosphate group from ATP to selected tyrosine side chains of the receptor itself and other specific second messenger proteins. Growth factors 15 (GF) that associate with receptor PTKs include epidermal GF, platelet-derived GF, fibroblast GF, hepatocyte GF, insulin and insulin-like GFs, nerve GF, vascular endothelial GF, and macrophage colony stimulating factor. Nontransmembrane PTKs form signaling complexes with the cytosolic domains of plasma membrane receptors. Receptors that signal through nontransmembrane PTKs include cytokine, hormone, and antigen-specific lymphocytic receptors. Many PTKs were first identified as oncogene products in cancer cells in which PTK activation was no longer subject to normal cellular controls. In fact, about one third of the known oncogenes encode PTKs. Furthermore, cellular transformation (oncogenesis) is often accompanied by increased tyrosine phosphorylation activity (Charbonneau, H. and Tonks, N. K. (1992) Annu. Rev. Cell Biol. 8:463-93). Regulation of PTK activity may therefore be an important strategy in controlling some types of cancer.

Some kinases utilize carbohydrates as their substrates and are important for glucose metabolism. For example, glycolysis employs four distinct kinases to effect the conversion of glucose to pyruvate, a key metabolite in the production of ATP. One of these enzymes is phosphofructokinase (PFK) which catalyzes the transfer of phosphate from ATP to fructose 6-30 phosphate. PFK is an allosteric enzyme and a key regulator of glycolysis. In certain genetic muscle disorders, such as muscle phosphofructokinase deficiency type VII, phosphofructokinase activity is absent in muscle and deficient in red blood cells. As a result, afflicted individuals suffer from mild hemolytic anemia and muscle pain (Isselbacher, K.J. et al. (1994) Harrison's Principles of Internal Medicine, McGraw-Hill, New York, NY, p. 2102).

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Kinase-mediated phosphorylation is antagonized by the activity of phosphatases, which

remove phosphate groups by hydrolysis. Phosphatases are classified into one of three evolutionarily distinct families: the protein serine/threonine phosphatases (PPs), the protein tyrosine phosphatases, and the acid/alkaline phosphatases. PPs may be further categorized into four distinct groups: PP-I, PP-IIA, PP-IIB, and PP-IIC. (Cohen, P. (1989) Annu. Rev. Biochem. 58:453-508). PP-I, in particular, dephosphorylates many of the proteins phosphorylated by PKA and is therefore an important regulator of signal transduction pathways. Kinase-activated proteins which bind to and inhibit PP-I have been identified. These inhibitors potentiate the activity of kinases such as PKA by allowing protein substrates to remain in their phosphorylated, activated state. A novel inhibitor of PP-1 has been purified from porcine aorta (Eto, M. et al. (1995) J. 10 Biochem. 118:1104-1107; Eto, M. et al. (1997) FEBS Lett. 410:356-360). This inhibitor, called CPI17, is 147 amino acids in length and is activated by PKC. CPI17 expression is restricted to smooth muscle tissues such as a rta and bladder, suggesting that CPI17 functions in PKCmediated signal transduction pathways in these tissues, possibly through a calcium-dependent mechanism.

The discovery of new phosphorylation effectors and the polynucleotides encoding them satisfies a need in the art by providing new compositions which are useful in the diagnosis. prevention, and treatment of cell proliferative, immune, and neuronal disorders.

# **SUMMARY OF THE INVENTION**

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The invention features substantially purified polypeptides, phosphorylation effectors, referred to collectively as "PHSP" and individually as "PHSP-1 to PHSP-31",. In one aspect, the invention provides a substantially purified polypeptide comprising an amino acid sequence selected from the group consisting of SEQ ID NO:1-31, and fragments thereof.

The invention further provides a substantially purified variant having at least 90% amino acid identity to at least one of the amino acid sequences selected from the group consisting of SEO ID NO:1-31, and fragments thereof. The invention also provides an isolated and purified polynucleotide encoding the polypeptide comprising an amino acid sequence selected from the group consisting of SEQ ID NO:1-31, and fragments thereof. The invention also includes an 30 isolated and purified polynucleotide variant having at least 80% polynucleotide sequence identity to the polynucleotide encoding the polypeptide comprising an amino acid sequence selected from the group consisting of SEQ ID NO:1-31, and fragments thereof.

Additionally, the invention provides an isolated and purified polynucleotide which hybridizes under stringent conditions to the polynucleotide encoding the polypeptide comprising an amino acid sequence selected from the group consisting of SEQ ID NO:1-31, and fragments

thereof. The invention also provides an isolated and purified polynucleotide having a sequence which is complementary to the polynucleotide encoding the polypeptide comprising the amino acid sequence selected from the group consisting of SEQ ID NO:1-31, and fragments thereof.

The invention also provides a method for detecting a polynucleotide in a sample 5 containing nucleic acids, the method comprising the steps of (a) hybridizing the complement of the polynucleotide sequence to at least one of the polynucleotides of the sample, thereby forming a hybridization complex; and (b) detecting the hybridization complex, wherein the presence of the hybridization complex correlates with the presence of a polynucleotide in the sample. In one aspect, the method further comprises amplifying the polynucleotide prior to hybridization.

The invention also provides an isolated and purified polynucleotide comprising a polynucleotide sequence selected from the group consisting of SEO ID NO:32-62, and fragments thereof. The invention further provides an isolated and purified polynucleotide variant having at least 80% polynucleotide sequence identity to the polynucleotide sequence selected from the group consisting of SEQ ID NO:32-62, and fragments thereof. The invention also provides an 15 isolated and purified polynucleotide having a sequence which is complementary to the polynucleotide comprising a polynucleotide sequence selected from the group consisting of SEQ ID NO:32-62, and fragments thereof.

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The invention further provides an expression vector containing at least a fragment of the polynucleotide encoding the polypeptide comprising an amino acid sequence selected from the 20 group consisting of SEQ ID NO:1-31, and fragments thereof. In another aspect, the expression vector is contained within a host cell.

The invention also provides a method for producing a polypeptide, the method comprising the steps of: (a) culturing the host cell containing an expression vector containing at least a fragment of a polynucleotide under conditions suitable for the expression of the polypeptide; and (b) recovering the polypeptide from the host cell culture.

The invention also provides a pharmaceutical composition comprising a substantially purified polypeptide having the amino acid sequence selected from the group consisting of SEQ ID NO:1-31, and fragments thereof, in conjunction with a suitable pharmaceutical carrier.

The invention further includes a purified antibody which binds to a polypeptide selected 30 from the group consisting of SEQ ID NO:1-31, and fragments thereof. The invention also provides a purified agonist and a purified antagonist to the polypeptide.

The invention also provides a method for treating or preventing a disorder associated with decreased expression or activity of PHSP, the method comprising administering to a subject in need of such treatment an effective amount of a pharmaceutical composition comprising a 35 substantially purified polypeptide having the amino acid sequence selected from the group



consisting of SEQ ID NO:1-31, and fragments thereof, in conjunction with a suitable pharmaceutical carrier.

The invention also provides a method for treating or preventing a disorder associated with increased expression or activity of PHSP, the method comprising administering to a subject in need of such treatment an effective amount of an antagonist of a polypeptide having an amino acid sequence selected from the group consisting of SEQ ID NO:1-31, and fragments thereof.

## **BRIEF DESCRIPTION OF THE TABLES**

Table 1 shows nucleotide and polypeptide sequence identification numbers (SEQ ID NO), clone identification numbers (clone ID), cDNA libraries, and cDNA fragments used to assemble full-length sequences encoding PHSP.

Table 2 shows features of each polypeptide sequence, including potential motifs, homologous sequences, and methods and algorithms used for identification of PHSP.

Table 3 shows the tissue-specific expression patterns of each nucleic acid sequence as
determined by northern analysis, diseases, disorders, or conditions associated with these tissues,
and the vector into which each cDNA was cloned.

Table 4 describes the tissues used to construct the cDNA libraries from which cDNA clones encoding PHSP were isolated.

Table 5 shows the tools, programs, and algorithms used to analyze PHSP, along with applicable descriptions, references, and threshold parameters.

# DESCRIPTION OF THE INVENTION

Before the present proteins, nucleotide sequences, and methods are described, it is understood that this invention is not limited to the particular machines, materials and methods described, as these may vary. It is also to be understood that the terminology used herein is for the purpose of describing particular embodiments only, and is not intended to limit the scope of the present invention which will be limited only by the appended claims.

It must be noted that as used herein and in the appended claims, the singular forms "a,"
"an," and "the" include plural reference unless the context clearly dictates otherwise. Thus, for
example, a reference to "a host cell" includes a plurality of such host cells, and a reference to "an
antibody" is a reference to one or more antibodies and equivalents thereof known to those skilled
in the art, and so forth.

Unless defined otherwise, all technical and scientific terms used herein have the same meanings as commonly understood by one of ordinary skill in the art to which this invention belongs. Although any machines, materials, and methods similar or equivalent to those described

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herein can be used to practice or test the present invention, the preferred machines, materials and methods are now described. All publications mentioned herein are cited for the purpose of describing and disclosing the cell lines, protocols, reagents and vectors which are reported in the publications and which might be used in connection with the invention. Nothing herein is to be construed as an admission that the invention is not entitled to antedate such disclosure by virtue of prior invention.

## **DEFINITIONS**

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"PHSP" refers to the amino acid sequences of substantially purified PHSP obtained from any species, particularly a mammalian species, including bovine, ovine, porcine, murine, equine, 10 and preferably the human species, from any source, whether natural, synthetic, semi-synthetic, or recombinant.

The term "agonist" refers to a molecule which, when bound to PHSP, increases or prolongs the duration of the effect of PHSP. Agonists may include proteins, nucleic acids, carbohydrates, or any other molecules which bind to and modulate the effect of PHSP.

An "allelic variant" is an alternative form of the gene encoding PHSP. Allelic variants may result from at least one mutation in the nucleic acid sequence and may result in altered mRNAs or in polypeptides whose structure or function may or may not be altered. Any given natural or recombinant gene may have none, one, or many allelic forms. Common mutational changes which give rise to allelic variants are generally ascribed to natural deletions, additions, or 20 substitutions of nucleotides. Each of these types of changes may occur alone, or in combination with the others, one or more times in a given sequence.

"Altered" nucleic acid sequences encoding PHSP include those sequences with deletions, insertions, or substitutions of different nucleotides, resulting in a polynucleotide the same as PHSP or a polypeptide with at least one functional characteristic of PHSP. Included within this 25 definition are polymorphisms which may or may not be readily detectable using a particular oligonucleotide probe of the polynucleotide encoding PHSP, and improper or unexpected hybridization to allelic variants, with a locus other than the normal chromosomal locus for the polynucleotide sequence encoding PHSP. The encoded protein may also be "altered," and may contain deletions, insertions, or substitutions of amino acid residues which produce a silent change 30 and result in a functionally equivalent PHSP. Deliberate amino acid substitutions may be made on the basis of similarity in polarity, charge, solubility, hydrophobicity, hydrophilicity, and/or the amphipathic nature of the residues, as long as the biological or immunological activity of PHSP is retained. For example, negatively charged amino acids may include aspartic acid and glutamic acid, positively charged amino acids may include lysine and arginine, and amino acids with 35 uncharged polar head groups having similar hydrophilicity values may include leucine, isoleucine,

and valine; glycine and alanine; asparagine and glutamine; serine and threonine; and phenylalanine and tyrosine.

The terms "amino acid" or "amino acid sequence" refer to an oligopeptide, peptide, polypeptide, or protein sequence, or a fragment of any of these, and to naturally occurring or synthetic molecules. In this context, "fragments," "immunogenic fragments," or "antigenic fragments" refer to fragments of PHSP which are preferably at least 5 to about 15 amino acids in length, most preferably at least 14 amino acids, and which retain some biological activity or immunological activity of PHSP. Where "amino acid sequence" is recited to refer to an amino acid sequence of a naturally occurring protein molecule, "amino acid sequence" and like terms are not meant to limit the amino acid sequence to the complete native amino acid sequence associated with the recited protein molecule.

"Amplification" relates to the production of additional copies of a nucleic acid sequence. Amplification is generally carried out using polymerase chain reaction (PCR) technologies well known in the art.

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The term "antagonist" refers to a molecule which, when bound to PHSP, decreases the amount or the duration of the effect of the biological or immunological activity of PHSP.

Antagonists may include proteins, nucleic acids, carbohydrates, antibodies, or any other molecules which decrease the effect of PHSP.

The term "antibody" refers to intact molecules as well as to fragments thereof, such as

Fab, F(ab')<sub>2</sub>, and Fv fragments, which are capable of binding the epitopic determinant. Antibodies that bind PHSP polypeptides can be prepared using intact polypeptides or using fragments containing small peptides of interest as the immunizing antigen. The polypeptide or oligopeptide used to immunize an animal (e.g., a mouse, a rat, or a rabbit) can be derived from the translation of RNA, or synthesized chemically, and can be conjugated to a carrier protein if desired. Commonly used carriers that are chemically coupled to peptides include bovine serum albumin, thyroglobulin, and keyhole limpet hemocyanin (KLH). The coupled peptide is then used to immunize the animal.

The term "antigenic determinant" refers to that fragment of a molecule (i.e., an epitope) that makes contact with a particular antibody. When a protein or a fragment of a protein is used to immunize a host animal, numerous regions of the protein may induce the production of antibodies which bind specifically to antigenic determinants (given regions or three-dimensional structures on the protein). An antigenic determinant may compete with the intact antigen (i.e., the immunogen used to elicit the immune response) for binding to an antibody.

The term "antisense" refers to any composition containing a nucleic acid sequence which is complementary to the "sense" strand of a specific nucleic acid sequence. Antisense molecules may be produced by any method including synthesis or transcription. Once introduced into a cell,

the complementary nucleotides combine with natural sequences produced by the cell to form duplexes and to block either transcription or translation. The designation "negative" can refer to the antisense strand, and the designation "positive" can refer to the sense strand.

The term "biologically active," refers to a protein having structural, regulatory, or biochemical functions of a naturally occurring molecule. Likewise, "immunologically active" refers to the capability of the natural, recombinant, or synthetic PHSP, or of any oligopeptide thereof, to induce a specific immune response in appropriate animals or cells and to bind with specific antibodies.

The terms "complementary" or "complementarity" refer to the natural binding of
polynucleotides by base pairing. For example, the sequence "5' A-G-T 3" bonds to the
complementary sequence "3' T-C-A 5'." Complementarity between two single-stranded molecules
may be "partial," such that only some of the nucleic acids bind, or it may be "complete," such that
total complementarity exists between the single stranded molecules. The degree of
complementarity between nucleic acid strands has significant effects on the efficiency and strength
of the hybridization between the nucleic acid strands. This is of particular importance in
amplification reactions, which depend upon binding between nucleic acids strands, and in the
design and use of peptide nucleic acid (PNA) molecules.

A "composition comprising a given polynucleotide sequence" or a "composition comprising a given amino acid sequence" refer broadly to any composition containing the given polynucleotide or amino acid sequence. The composition may comprise a dry formulation or an aqueous solution. Compositions comprising polynucleotide sequences encoding PHSP or fragments of PHSP may be employed as hybridization probes. The probes may be stored in freezedried form and may be associated with a stabilizing agent such as a carbohydrate. In hybridizations, the probe may be deployed in an aqueous solution containing salts (e.g., NaCl), detergents (e.g., sodium dodecyl sulfate; SDS), and other components (e.g., Denhardt's solution, dry milk, salmon sperm DNA, etc.).

"Consensus sequence" refers to a nucleic acid sequence which has been resequenced to resolve uncalled bases, extended using the XL-PCR kit (Perkin-Elmer, Norwalk CT) in the 5' and/or the 3' direction, and resequenced, or which has been assembled from the overlapping sequences of more than one Incyte Clone using a computer program for fragment assembly, such as the GELVIEW fragment assembly system (GCG, Madison WI). Some sequences have been both extended and assembled to produce the consensus sequence.

The term "correlates with expression of a polynucleotide" indicates that the detection of the presence of nucleic acids, the same or related to a nucleic acid sequence encoding PHSP, by northern analysis is indicative of the presence of nucleic acids encoding PHSP in a sample, and

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thereby correlates with expression of the transcript from the polynucleotide encoding PHSP.

A "deletion" refers to a change in the amino acid or nucleotide sequence that results in the absence of one or more amino acid residues or nucleotides.

The term "derivative" refers to the chemical modification of a polypeptide sequence, or a

5 polynucleotide sequence. Chemical modifications of a polynucleotide sequence can include, for
example, replacement of hydrogen by an alkyl, acyl, or amino group. A derivative polynucleotide
encodes a polypeptide which retains at least one biological or immunological function of the
natural molecule. A derivative polypeptide is one modified by glycosylation, pegylation, or any
similar process that retains at least one biological or immunological function of the polypeptide

from which it was derived.

The term "similarity" refers to a degree of complementarity. There may be partial similarity or complete similarity. The word "identity" may substitute for the word "similarity." A partially complementary sequence that at least partially inhibits an identical sequence from hybridizing to a target nucleic acid is referred to as "substantially similar." The inhibition of hybridization of the completely complementary sequence to the target sequence may be examined using a hybridization assay (Southern or northern blot, solution hybridization, and the like) under conditions of reduced stringency. A substantially similar sequence or hybridization probe will compete for and inhibit the binding of a completely similar (identical) sequence to the target sequence under conditions of reduced stringency. This is not to say that conditions of reduced stringency are such that non-specific binding is permitted, as reduced stringency conditions require that the binding of two sequences to one another be a specific (i.e., a selective) interaction. The absence of non-specific binding may be tested by the use of a second target sequence which lacks even a partial degree of complementarity (e.g., less than about 30% similarity or identity). In the absence of non-specific binding, the substantially similar sequence or probe will not hybridize to the second non-complementary target sequence.

The phrases "percent identity" and "% identity" refer to the percentage of sequence similarity found in a comparison of two or more amino acid or nucleic acid sequences. Percent identity can be determined electronically, e.g., by using the MEGALIGN program (DNASTAR, Madison WI) which creates alignments between two or more sequences according to methods selected by the user, e.g., the clustal method. (See, e.g., Higgins, D.G. and P.M. Sharp (1988) Gene 73:237-244.) The clustal algorithm groups sequences into clusters by examining the distances between all pairs. The clusters are aligned pairwise and then in groups. The percentage similarity between two amino acid sequences, e.g., sequence A and sequence B, is calculated by dividing the length of sequence A, minus the number of gap residues in sequence A, minus the number of gap residues in sequence A

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and sequence B, times one hundred. Gaps of low or of no similarity between the two amino acid sequences are not included in determining percentage similarity. Percent identity between nucleic acid sequences can also be counted or calculated by other methods known in the art, e.g., the Jotun Hein method. (See, e.g., Hein, J. (1990) Methods Enzymol. 183:626-645.) Identity between sequences can also be determined by other methods known in the art, e.g., by varying hybridization conditions.

"Human artificial chromosomes" (HACs) are linear microchromosomes which may contain DNA sequences of about 6 kb to 10 Mb in size, and which contain all of the elements required for stable mitotic chromosome segregation and maintenance.

The term "humanized antibody" refers to antibody molecules in which the amino acid sequence in the non-antigen binding regions has been altered so that the antibody more closely resembles a human antibody, and still retains its original binding ability.

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"Hybridization" refers to any process by which a strand of nucleic acid binds with a complementary strand through base pairing.

The term "hybridization complex" refers to a complex formed between two nucleic acid sequences by virtue of the formation of hydrogen bonds between complementary bases. A hybridization complex may be formed in solution (e.g.,  $C_0$ t or  $R_0$ t analysis) or formed between one nucleic acid sequence present in solution and another nucleic acid sequence immobilized on a solid support (e.g., paper, membranes, filters, chips, pins or glass slides, or any other appropriate substrate to which cells or their nucleic acids have been fixed).

The words "insertion" or "addition" refer to changes in an amino acid or nucleotide sequence resulting in the addition of one or more amino acid residues or nucleotides, respectively, to the sequence found in the naturally occurring molecule.

"Immune response" can refer to conditions associated with inflammation, trauma, immune disorders, or infectious or genetic disease, etc. These conditions can be characterized by expression of various factors, e.g., cytokines, chemokines, and other signaling molecules, which may affect cellular and systemic defense systems.

The term "microarray" refers to an arrangement of distinct polynucleotides on a substrate.

The terms "element" or "array element" in a microarray context, refer to hybridizable polynucleotides arranged on the surface of a substrate.

The term "modulate" refers to a change in the activity of PHSP. For example, modulation may cause an increase or a decrease in protein activity, binding characteristics, or any other biological, functional, or immunological properties of PHSP.

The phrases "nucleic acid" or "nucleic acid sequence," as used herein, refer to a nucleotide, oligonucleotide, polynucleotide, or any fragment thereof. These phrases also refer to

DNA or RNA of genomic or synthetic origin which may be single-stranded or double-stranded and may represent the sense or the antisense strand, to peptide nucleic acid (PNA), or to any DNA-like or RNA-like material. In this context, "fragments" refers to those nucleic acid sequences which, comprise a region of unique polynucleotide sequence that specifically identifies SEQ ID NO:32-62, for example, as distinct from any other sequence in the same genome. For example, a fragment of SEQ ID NO:32-62 is useful in hybridization and amplification technologies and in analogous methods that distinguish SEQ ID NO:32-62 from related polynucleotide sequences. A fragment of SEQ ID NO:32-62 is at least about 15-20 nucleotides in length. The precise length of the fragment of SEQ ID NO:32-62 and the region of SEQ ID NO:32-62 to which the fragment corresponds are routinely determinable by one of ordinary skill in the art based on the intended purpose for the fragment. In some cases, a fragment, when translated, would produce polypeptides retaining some functional characteristic, e.g., antigenicity, or structural domain characteristic, e.g., ATP-binding site, of the full-length polypeptide

The terms "operably associated" or "operably linked" refer to functionally related nucleic acid sequences. A promoter is operably associated or operably linked with a coding sequence if the promoter controls the translation of the encoded polypeptide. While operably associated or operably linked nucleic acid sequences can be contiguous and in the same reading frame, certain genetic elements, e.g., repressor genes, are not contiguously linked to the sequence encoding the polypeptide but still bind to operator sequences that control expression of the polypeptide.

The term "oligonucleotide" refers to a nucleic acid sequence of at least about 6 nucleotides to 60 nucleotides, preferably about 15 to 30 nucleotides, and most preferably about 20 to 25 nucleotides, which can be used in PCR amplification or in a hybridization assay or microarray. "Oligonucleotide" is substantially equivalent to the terms "amplimer," "primer," "oligomer," and "probe," as these terms are commonly defined in the art.

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"Peptide nucleic acid" (PNA) refers to an antisense molecule or anti-gene agent which comprises an oligonucleotide of at least about 5 nucleotides in length linked to a peptide backbone of amino acid residues ending in lysine. The terminal lysine confers solubility to the composition. PNAs preferentially bind complementary single stranded DNA or RNA and stop transcript elongation, and may be pegylated to extend their lifespan in the cell.

The term "sample" is used in its broadest sense. A sample suspected of containing nucleic acids encoding PHSP, or fragments thereof, or PHSP itself, may comprise a bodily fluid; an extract from a cell, chromosome, organelle, or membrane isolated from a cell; a cell; genomic DNA, RNA, or cDNA, in solution or bound to a substrate; a tissue; a tissue print; etc.

The terms "specific binding" or "specifically binding" refer to that interaction between a protein or peptide and an agonist, an antibody, or an antagonist. The interaction is dependent upon

the presence of a particular structure of the protein, e.g., the antigenic determinant or epitope, recognized by the binding molecule. For example, if an antibody is specific for epitope "A," the presence of a polypeptide containing the epitope A, or the presence of free unlabeled A, in a reaction containing free labeled A and the antibody will reduce the amount of labeled A that binds to the antibody.

The term "stringent conditions" refers to conditions which permit hybridization between polynucleotides and the claimed polynucleotides. Stringent conditions can be defined by salt concentration, the concentration of organic solvent, e.g., formamide, temperature, and other conditions well known in the art. In particular, stringency can be increased by reducing the concentration of salt, increasing the concentration of formamide, or raising the hybridization temperature.

The term "substantially purified" refers to nucleic acid or amino acid sequences that are removed from their natural environment and are isolated or separated, and are at least about 60% free, preferably about 75% free, and most preferably about 90% free from other components with which they are naturally associated.

A "substitution" refers to the replacement of one or more amino acids or nucleotides by different amino acids or nucleotides, respectively.

"Substrate" refers to any suitable rigid or semi-rigid support including membranes, filters, chips, slides, wafers, fibers, magnetic or nonmagnetic beads, gels, tubing, plates, polymers, microparticles and capillaries. The substrate can have a variety of surface forms, such as wells, trenches, pins, channels and pores, to which polynucleotides or polypeptides are bound.

"Transformation" describes a process by which exogenous DNA enters and changes a recipient cell. Transformation may occur under natural or artificial conditions according to various methods well known in the art, and may rely on any known method for the insertion of foreign nucleic acid sequences into a prokaryotic or eukaryotic host cell. The method for transformation is selected based on the type of host cell being transformed and may include, but is not limited to, viral infection, electroporation, heat shock, lipofection, and particle bombardment. The term "transformed" cells includes stably transformed cells in which the inserted DNA is capable of replication either as an autonomously replicating plasmid or as part of the host chromosome, as well as transiently transformed cells which express the inserted DNA or RNA for limited periods of time.

A "variant" of PHSP polypeptides refers to an amino acid sequence that is altered by one or more amino acid residues. The variant may have "conservative" changes, wherein a substituted amino acid has similar structural or chemical properties (e.g., replacement of leucine with isoleucine). More rarely, a variant may have "nonconservative" changes (e.g., replacement of

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glycine with tryptophan). Analogous minor variations may also include amino acid deletions or insertions, or both. Guidance in determining which amino acid residues may be substituted, inserted, or deleted without abolishing biological or immunological activity may be found using computer programs well known in the art, for example, LASERGENE software (DNASTAR).

The term "variant," when used in the context of a polynucleotide sequence, may encompass a polynucleotide sequence related to PHSP. This definition may also include, for example, "allelic" (as defined above), "splice," "species," or "polymorphic" variants. A splice variant may have significant identity to a reference molecule, but will generally have a greater or lesser number of polynucleotides due to alternate splicing of exons during mRNA processing. The 10 corresponding polypeptide may possess additional functional domains or an absence of domains. Species variants are polynucleotide sequences that vary from one species to another. The resulting polypeptides generally will have significant amino acid identity relative to each other. A polymorphic variant is a variation in the polynucleotide sequence of a particular gene between individuals of a given species. Polymorphic variants also may encompass "single nucleotide 15 polymorphisms" (SNPs) in which the polynucleotide sequence varies by one base. The presence of SNPs may be indicative of, for example, a certain population, a disease state, or a propensity for a disease state.

### THE INVENTION

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The invention is based on the discovery of new human phosphorylation effectors (PHSP), 20 the polynucleotides encoding PHSP, and the use of these compositions for the diagnosis, treatment, or prevention of cell proliferative, immune, and neuronal disorders.

Table 1 lists the Incyte clones used to assemble full length nucleotide sequences encoding PHSP. Columns 1 and 2 show the sequence identification numbers (SEQ ID NOs) of the polypeptide and nucleotide sequences, respectively. Column 3 shows the clone IDs of the Incyte 25 clones in which nucleic acids encoding each PHSP were identified, and column 4 shows the cDNA libraries from which these clones were isolated. Column 5 shows Incyte clones and their corresponding cDNA libraries. Clones for which cDNA libraries are not indicated were derived from pooled cDNA libraries. The clones in column 5 were used to assemble the consensus nucleotide sequence of each PHSP and are useful as fragments in hybridization technologies.

The columns of Table 2 show various properties of each of the polypeptides of the invention: column 1 references the SEQ ID NO and column 2 shows the number of amino acid residues in each polypeptide. Columns 3 and 4 show potential phosphorylation sites and potential glycosylation sites, respectively. Column 5 shows the amino acid residues comprising signature sequences and motifs. Column 6 shows homologous sequences as identified by BLAST analysis, 35 while column 7 shows analytical methods used to identify each polypeptide through sequence

homology and protein motifs.

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The columns of Table 3 show the tissue-specificity and diseases, disorders, or conditions associated with nucleotide sequences encoding PHSP. The first column of Table 3 lists the SEQ ID NOs. Column 2 lists tissue categories which express PHSP as a fraction of total tissue categories expressing PHSP. Column 3 lists diseases, disorders, or conditions associated with those tissues expressing PHSP. Column 4 lists the vectors used to subclone the cDNA library.

The columns of Table 4 show descriptions of the tissues used to construct the cDNA libraries from which cDNA clones encoding PHSP were isolated. Column 1 references the SEQ ID NO, column 2 shows the cDNA libraries from which these clones were isolated, and column 3 shows the tissue origins and other descriptive information relevant to the cDNA libraries in column 2.

The following fragments of the nucleotide sequences encoding PHSP are useful, for example, in hybridization or amplification technologies to identify SEQ ID NO:32-62 and to distinguish between SEQ ID NO:32-62 and related polynucleotide sequences. The useful 15 fragments include, the fragment of SEQ ID NO:32 from about nucleotide 81 to about nucleotide 110; the fragment of SEQ ID NO:33 from about nucleotide 323 to about nucleotide 352; the fragment of SEQ ID NO:34 from about nucleotide 83 to about nucleotide 112; the fragment of SEQ ID NO:35 from about nucleotide 524 to about nucleotide 553; the fragment of SEQ ID NO:36 from about nucleotide 275 to about nucleotide 346; the fragment of SEQ ID NO:37 from about nucleotide 1328 to about nucleotide 1396; the fragment of SEQ ID NO:38 from about nucleotide 245 to about nucleotide 304; the fragment of SEQ ID NO:39 from about nucleotide 1253 to about nucleotide 1312; the fragment of SEQ ID NO:41 from about nucleotide 117 to about nucleotide 170; the fragments of SEQ ID NO:42 from about nucleotide 109 to about nucleotide 153, and from about nucleotide 325 to about nucleotide 369; the fragments of SEQ ID NO:43 from 25 about nucleotide 380 to about nucleotide 424, and from about nucleotide 1190 to about nucleotide 1234; the fragment of SEQ ID NO:44 from about nucleotide 1 to about nucleotide 46; the fragment of SEQ ID NO:45 from about nucleotide 533 to about nucleotide 577; the fragments of SEQ ID NO:46 from about nucleotide 109 to about nucleotide 153, and from about nucleotide 379 to about nucleotide 423; the fragment of SEQ ID NO:47 from about nucleotide 1730 to about 30 nucleotide 1774; the fragment of SEQ ID NO:48 from about nucleotide 433 to about nucleotide 477; the fragment of SEQ ID NO:49 from about nucleotide 1117 to about nucleotide 1155; the fragment of SEQ ID NO:50 from about nucleotide 166 to about nucleotide 213; the fragment of SEQ ID NO:51 from about nucleotide 60 to about nucleotide 95; the fragment of SEQ ID NO:52 from about nucleotide 326 to about nucleotide 370; the fragment of SEQ ID NO:53 from about 35 nucleotide 25 to about nucleotide 66; the fragment of SEQ ID NO:54 from about nucleotide 55 to

about nucleotide 102; the fragment of SEQ ID NO:55 from about nucleotide 138 to about nucleotide 167; the fragment of SEQ ID NO:56 from about nucleotide 29 to about nucleotide 58; the fragment of SEQ ID NO:57 from about nucleotide 455 to about nucleotide 484; the fragment of SEQ ID NO:58 from about nucleotide 226 to about nucleotide 255; the fragment of SEQ ID NO:59 from about nucleotide 557 to about nucleotide 598; the fragment of SEQ ID NO:60 from about nucleotide 284 to about nucleotide 325; the fragment of SEQ ID NO:61 from about nucleotide 1043 to about nucleotide 1090; and the fragment of SEQ ID NO:62 from about nucleotide 84 to about nucleotide 132. The polypeptides encoded by the fragments of SEQ ID NO:32-62 are useful, for example, as immunogenic peptides.

The invention also encompasses PHSP variants. A preferred PHSP variant is one which has at least about 80%, more preferably at least about 90%, and most preferably at least about 95% amino acid sequence identity to the PHSP amino acid sequence, and which contains at least one functional or structural characteristic of PHSP.

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The invention also encompasses polynucleotides which encode PHSP. In a particular embodiment, the invention encompasses a polynucleotide sequence comprising a sequence selected from the group consisting of SEQ ID NO:32-62, which encodes PHSP.

The invention also encompasses a variant of a polynucleotide sequence encoding PHSP. In particular, such a variant polynucleotide sequence will have at least about 80%, more preferably at least about 85%, and most preferably at least about 95% polynucleotide sequence identity to the polynucleotide sequence encoding PHSP. A particular aspect of the invention encompasses a variant of a polynucleotide sequence comprising a sequence selected from the group consisting of SEQ ID NO:32-62 which has at least about 80%, more preferably at least about 85%, and most preferably at least about 95% polynucleotide sequence identity to a nucleic acid sequence selected from the group consisting of SEQ ID NO:32-62. Any one of the polynucleotide variants described above can encode an amino acid sequence which contains at least one functional or structural characteristic of PHSP.

It will be appreciated by those skilled in the art that as a result of the degeneracy of the genetic code, a multitude of polynucleotide sequences encoding PHSP, some bearing minimal similarity to the polynucleotide sequences of any known and naturally occurring gene, may be produced. Thus, the invention contemplates each and every possible variation of polynucleotide sequence that could be made by selecting combinations based on possible codon choices. These combinations are made in accordance with the standard triplet genetic code as applied to the polynucleotide sequence of naturally occurring PHSP, and all such variations are to be considered as being specifically disclosed.

Although nucleotide sequences which encode PHSP and its variants are preferably capable of hybridizing to the nucleotide sequence of the naturally occurring PHSP under appropriately selected conditions of stringency, it may be advantageous to produce nucleotide sequences encoding

PHSP or its derivatives possessing a substantially different codon usage, e.g., inclusion of non-naturally occurring codons. Codons may be selected to increase the rate at which expression of the peptide occurs in a particular prokaryotic or eukaryotic host in accordance with the frequency with which particular codons are utilized by the host. Other reasons for substantially altering the nucleotide sequence encoding PHSP and its derivatives without altering the encoded amino acid sequences include the production of RNA transcripts having more desirable properties, such as a greater half-life, than transcripts produced from the naturally occurring sequence.

The invention also encompasses production of DNA sequences which encode PHSP and PHSP derivatives, or fragments thereof, entirely by synthetic chemistry. After production, the synthetic sequence may be inserted into any of the many available expression vectors and cell systems using reagents well known in the art. Moreover, synthetic chemistry may be used to introduce mutations into a sequence encoding PHSP or any fragment thereof.

Also encompassed by the invention are polynucleotide sequences that are capable of hybridizing to the claimed polynucleotide sequences, and, in particular, to those shown in SEO ID 15 NO:32-62 and fragments thereof under various conditions of stringency. (See, e.g., Wahl, G.M. and S.L. Berger (1987) Methods Enzymol. 152:399-407; Kimmel, A.R. (1987) Methods Enzymol. 152:507-511.) For example, stringent salt concentration will ordinarily be less than about 750 mM NaCl and 75 mM trisodium citrate, preferably less than about 500 mM NaCl and 50 mM trisodium citrate, and most preferably less than about 250 mM NaCl and 25 mM trisodium citrate. Low 20 stringency hybridization can be obtained in the absence of organic solvent, e.g., formamide, while high stringency hybridization can be obtained in the presence of at least about 35% formamide, and most preferably at least about 50% formamide. Stringent temperature conditions will ordinarily include temperatures of at least about 30°C, more preferably of at least about 37°C, and most preferably of at least about 42°C. Varying additional parameters, such as hybridization time, the 25 concentration of detergent, e.g., sodium dodecyl sulfate (SDS), and the inclusion or exclusion of carrier DNA, are well known to those skilled in the art. Various levels of stringency are accomplished by combining these various conditions as needed. In a preferred embodiment, hybridization will occur at 30°C in 750 mM NaCl, 75 mM trisodium citrate, and 1% SDS. In a more preferred embodiment, hybridization will occur at 37°C in 500 mM NaCl, 50 mM trisodium citrate, 1% SDS, 35% 30 formamide, and 100 µg/ml denatured salmon sperm DNA (ssDNA). In a most preferred embodiment, hybridization will occur at 42°C in 250 mM NaCl, 25 mM trisodium citrate, 1% SDS, 50 % formamide, and 200  $\mu$ g/ml ssDNA. Useful variations on these conditions will be readily apparent to those skilled in the art.

The washing steps which follow hybridization can also vary in stringency. Wash stringency conditions can be defined by salt concentration and by temperature. As above, wash stringency can

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be increased by decreasing salt concentration or by increasing temperature. For example, stringent salt concentration for the wash steps will preferably be less than about 30 mM NaCl and 3 mM trisodium citrate, and most preferably less than about 15 mM NaCl and 1.5 mM trisodium citrate. Stringent temperature conditions for the wash steps will ordinarily include temperature of at least about 25°C, more preferably of at least about 42°C, and most preferably of at least about 68°C. In a preferred embodiment, wash steps will occur at 25°C in 30 mM NaCl, 3 mM trisodium citrate, and 0.1% SDS. In a more preferred embodiment, wash steps will occur at 42°C in 15 mM NaCl, 1.5 mM trisodium citrate, and 0.1% SDS. In a most preferred embodiment, wash steps will occur at 68°C in 15 mM NaCl, 1.5 mM trisodium citrate, and 0.1% SDS. Additional variations on these conditions will be readily apparent to those skilled in the art.

Methods for DNA sequencing are well known in the art and may be used to practice any of the embodiments of the invention. The methods may employ such enzymes as the Klenow fragment of DNA polymerase I, SEQUENASE (US Biochemical, Cleveland OH), Taq polymerase (Perkin-Elmer), thermostable T7 polymerase (Amersham Pharmacia Biotech, Piscataway NJ), or combinations of polymerases and proofreading exonucleases such as those found in the ELONGASE amplification system (Life Technologies, Gaithersburg MD). Preferably, sequence preparation is automated with machines such as the MICROLAB 2200 (Hamilton, Reno NV), Peltier thermal cycler 200 (PTC200; MJ Research, Watertown MA) and the ABI CATALYST 800 (Perkin-Elmer). Sequencing is then carried out using the ABI 373 or 377 DNA sequencing systems (Perkin-Elmer), or the MEGABACE 1000 DNA sequencing system (Molecular Dynamics, Sunnyvale CA), or other systems known in the art. The resulting sequences are analyzed using a variety of algorithms which are well known in the art. (See, e.g., Ausubel, F.M. (1997) Short Protocols in Molecular Biology, John Wiley & Sons, New York NY, unit 7.7; Meyers, R.A. (1995) Molecular Biology and Biotechnology, Wiley VCH, New York NY, pp. 856-853.)

The nucleic acid sequences encoding PHSP may be extended utilizing a partial nucleotide sequence and employing various PCR-based methods known in the art to detect upstream sequences, such as promoters and regulatory elements. For example, one method which may be employed, restriction-site PCR, uses universal and nested primers to amplify unknown sequence from genomic DNA within a cloning vector. (See, e.g., Sarkar, G. (1993) PCR Methods Applic. 2:318-322.)

Another method, inverse PCR, uses primers that extend in divergent directions to amplify unknown sequence from a circularized template. The template is derived from restriction fragments comprising a known genomic locus and surrounding sequences. (See, e.g., Triglia, T. et al. (1988) Nucleic Acids Res. 16:8186.) A third method, capture PCR, involves PCR amplification of DNA fragments adjacent to known sequences in human and yeast artificial chromosome DNA. (See, e.g., Lagerstrom, M. et al. (1991) PCR Methods Applic. 1:111-119.) In this method, multiple restriction enzyme digestions

and ligations may be used to insert an engineered double-stranded sequence into a region of unknown sequence before performing PCR. Other methods which may be used to retrieve unknown sequences are known in the art. (See, e.g., Parker, J.D. et al. (1991) Nucleic Acids Res. 19:3055-306). Additionally, one may use PCR, nested primers, and PROMOTERFINDER libraries (Clontech, Palo Alto CA) to walk genomic DNA. This procedure avoids the need to screen libraries and is useful in finding intron/exon junctions. For all PCR-based methods, primers may be designed using commercially available software, such as OLIGO 4.06 primer analysis software (National Biosciences, Plymouth MN) or another appropriate program, to be about 22 to 30 nucleotides in length, to have a GC content of about 50% or more, and to anneal to the template at temperatures of about 68°C to 72°C.

When screening for full-length cDNAs, it is preferable to use libraries that have been size-selected to include larger cDNAs. In addition, random-primed libraries, which often include sequences containing the 5' regions of genes, are preferable for situations in which an oligo d(T) library does not yield a full-length cDNA. Genomic libraries may be useful for extension of sequence into 5' non-transcribed regulatory regions.

Capillary electrophoresis systems which are commercially available may be used to analyze the size or confirm the nucleotide sequence of sequencing or PCR products. In particular, capillary sequencing may employ flowable polymers for electrophoretic separation, four different nucleotide-specific, laser-stimulated fluorescent dyes, and a charge coupled device camera for detection of the emitted wavelengths. Output/light intensity may be converted to electrical signal using appropriate software (e.g., GENOTYPER and SEQUENCENAVIGATOR, Perkin-Elmer), and the entire process from loading of samples to computer analysis and electronic data display may be computer controlled. Capillary electrophoresis is especially preferable for sequencing small DNA fragments which may be present in limited amounts in a particular sample.

In another embodiment of the invention, polynucleotide sequences or fragments thereof which encode PHSP may be cloned in recombinant DNA molecules that direct expression of PHSP, or fragments or functional equivalents thereof, in appropriate host cells. Due to the inherent degeneracy of the genetic code, other DNA sequences which encode substantially the same or a functionally equivalent amino acid sequence may be produced and used to express PHSP.

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The nucleotide sequences of the present invention can be engineered using methods generally known in the art in order to alter PHSP-encoding sequences for a variety of purposes including, but not limited to, modification of the cloning, processing, and/or expression of the gene product. DNA shuffling by random fragmentation and PCR reassembly of gene fragments and synthetic oligonucleotides may be used to engineer the nucleotide sequences. For example, oligonucleotide-mediated site-directed mutagenesis may be used to introduce mutations that create new restriction

sites, alter glycosylation patterns, change codon preference, produce splice variants, and so forth.

In another embodiment, sequences encoding PHSP may be synthesized, in whole or in part, using chemical methods well known in the art. (See, e.g., Caruthers, M.H. et al. (1980) Nucl. Acids Res. Symp. Ser. 215-223, and Horn, T. et al. (1980) Nucl. Acids Res. Symp. Ser. 225-232.)

5 Alternatively, PHSP itself or a fragment thereof may be synthesized using chemical methods. For example, peptide synthesis can be performed using various solid-phase techniques. (See, e.g., Roberge, J.Y. et al. (1995) Science 269:202-204.) Automated synthesis may be achieved using the ABI 431A Peptide Synthesizer (Perkin-Elmer). Additionally, the amino acid sequence of PHSP, or any part thereof, may be altered during direct synthesis and/or combined with sequences from other proteins, or any part thereof, to produce a variant polypeptide.

The peptide may be substantially purified by preparative high performance liquid chromatography. (See, e.g, Chiez, R.M. and F.Z. Regnier (1990) Methods Enzymol. 182:392-421.)

The composition of the synthetic peptides may be confirmed by amino acid analysis or by sequencing. (See, e.g., Creighton, T. (1984) Proteins, Structures and Molecular Properties, WH Freeman, New York NY.)

In order to express a biologically active PHSP, the nucleotide sequences encoding PHSP or derivatives thereof may be inserted into an appropriate expression vector, i.e., a vector which contains the necessary elements for transcriptional and translational control of the inserted coding sequence in a suitable host. These elements include regulatory sequences, such as enhancers, constitutive and 20 inducible promoters, and 5' and 3' untranslated regions in the vector and in polynucleotide sequences encoding PHSP. Such elements may vary in their strength and specificity. Specific initiation signals may also be used to achieve more efficient translation of sequences encoding PHSP. Such signals include the ATG initiation codon and adjacent sequences, e.g. the Kozak sequence. In cases where sequences encoding PHSP and its initiation codon and upstream regulatory sequences are inserted into 25 the appropriate expression vector, no additional transcriptional or translational control signals may be needed. However, in cases where only coding sequence, or a fragment thereof, is inserted, exogenous translational control signals including an in-frame ATG initiation codon should be provided by the vector. Exogenous translational elements and initiation codons may be of various origins, both natural and synthetic. The efficiency of expression may be enhanced by the inclusion of enhancers appropriate for the particular host cell system used. (See, e.g., Scharf, D. et al. (1994) Results Probl. Cell Differ. 20:125-162.)

Methods which are well known to those skilled in the art may be used to construct expression vectors containing sequences encoding PHSP and appropriate transcriptional and translational control elements. These methods include <u>in vitro</u> recombinant DNA techniques, synthetic techniques, and <u>in vivo</u> genetic recombination. (See, e.g., Sambrook, J. et al. (1989) Molecular Cloning, A Laboratory

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Manual, Cold Spring Harbor Press, Plainview NY, ch. 4, 8, and 16-17; Ausubel, F.M. et al. (1995) Current Protocols in Molecular Biology, John Wiley & Sons, New York NY, ch. 9, 13, and 16.)

A variety of expression vector/host systems may be utilized to contain and express sequences encoding PHSP. These include, but are not limited to, microorganisms such as bacteria transformed with recombinant bacteriophage, plasmid, or cosmid DNA expression vectors; yeast transformed with yeast expression vectors; insect cell systems infected with viral expression vectors (e.g., baculovirus); plant cell systems transformed with viral expression vectors (e.g., cauliflower mosaic virus, CaMV, or tobacco mosaic virus, TMV) or with bacterial expression vectors (e.g., Ti or pBR322 plasmids); or animal cell systems. The invention is not limited by the host cell employed.

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In bacterial systems, a number of cloning and expression vectors may be selected depending upon the use intended for polynucleotide sequences encoding PHSP. For example, routine cloning, subcloning, and propagation of polynucleotide sequences encoding PHSP can be achieved using a multifunctional E. coli vector such as PBLUESCRIPT (Stratagene, La Jolla CA) or pSPORT1 plasmid (Life Technologies). Ligation of sequences encoding PHSP into the vector's multiple cloning site 15 disrupts the lacZ gene, allowing a colorimetric screening procedure for identification of transformed bacteria containing recombinant molecules. In addition, these vectors may be useful for in vitro transcription, dideoxy sequencing, single strand rescue with helper phage, and creation of nested deletions in the cloned sequence. (See, e.g., Van Heeke, G. and S.M. Schuster (1989) J. Biol. Chem. 264:5503-5509.) When large quantities of PHSP are needed, e.g. for the production of antibodies, 20 vectors which direct high level expression of PHSP may be used. For example, vectors containing the strong, inducible T5 or T7 bacteriophage promoter may be used.

Yeast expression systems may be used for production of PHSP. A number of vectors containing constitutive or inducible promoters, such as alpha factor, alcohol oxidase, and PGH, may be used in the yeast Saccharomyces cerevisiae or Pichia pastoris. In addition, such vectors direct either the secretion or intracellular retention of expressed proteins and enable integration of foreign sequences into the host genome for stable propagation. (See, e.g., Ausubel, 1995, supra; Grant et al. (1987) Methods Enzymol. 153:516-54; and Scorer, C. A. et al. (1994) Bio/Technology 12:181-184.)

Plant systems may also be used for expression of PHSP. Transcription of sequences encoding PHSP may be driven viral promoters, e.g., the 35S and 19S promoters of CaMV used alone or in 30 combination with the omega leader sequence from TMV (Takamatsu, N. (1987) EMBO J. 6:307-311). Alternatively, plant promoters such as the small subunit of RUBISCO or heat shock promoters may be used. (See, e.g., Coruzzi, G. et al. (1984) EMBO J. 3:1671-1680; Broglie, R. et al. (1984) Science 224:838-843; and Winter, J. et al. (1991) Results Probl. Cell Differ. 17:85-105.) These constructs can be introduced into plant cells by direct DNA transformation or pathogen-mediated transfection. (See, 35 e.g., The McGraw Hill Yearbook of Science and Technology (1992) McGraw Hill, New York NY,

pp. 191-196.)

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In mammalian cells, a number of viral-based expression systems may be utilized. In cases where an adenovirus is used as an expression vector, sequences encoding PHSP may be ligated into an adenovirus transcription/translation complex consisting of the late promoter and tripartite leader sequence. Insertion in a non-essential E1 or E3 region of the viral genome may be used to obtain infective virus which expresses PHSP in host cells. (See, e.g., Logan, J. and T. Shenk (1984) Proc. Natl. Acad. Sci. 81:3655-3659.) In addition, transcription enhancers, such as the Rous sarcoma virus (RSV) enhancer, may be used to increase expression in mammalian host cells. SV40 or EBV-based vectors may also be used for high-level protein expression.

Human artificial chromosomes (HACs) may also be employed to deliver larger fragments of DNA than can be contained in and expressed from a plasmid. HACs of about 6 kb to 10 Mb are constructed and delivered via conventional delivery methods (liposomes, polycationic amino polymers, or vesicles) for therapeutic purposes. (See, e.g., Harrington, J.J. et al. (1997) Nat Genet. 15:345-355.)

For long term production of recombinant proteins in mammalian systems, stable expression of PHSP in cell lines is preferred. For example, sequences encoding PHSP can be transformed into cell lines using expression vectors which may contain viral origins of replication and/or endogenous expression elements and a selectable marker gene on the same or on a separate vector. Following the introduction of the vector, cells may be allowed to grow for about 1 to 2 days in enriched media before being switched to selective media. The purpose of the selectable marker is to confer resistance to a selective agent, and its presence allows growth and recovery of cells which successfully express the introduced sequences. Resistant clones of stably transformed cells may be propagated using tissue culture techniques appropriate to the cell type.

Any number of selection systems may be used to recover transformed cell lines. These include, but are not limited to, the herpes simplex virus thymidine kinase and adenine phosphoribosyltransferase genes, for use in *tk* or *apr* cells, respectively. (See, e.g., Wigler, M. et al. (1977) Cell 11:223-232; Lowy, I. et al. (1980) Cell 22:817-823.) Also, antimetabolite, antibiotic, or herbicide resistance can be used as the basis for selection. For example, *dhfr* confers resistance to methotrexate; *neo* confers resistance to the aminoglycosides, neomycin and G-418; and *als* or *pat* confer resistance to chlorsulfuron and phosphinotricin acetyltransferase, respectively. (See, e.g., Wigler, M. et al. (1980) Proc. Natl. Acad. Sci. 77:3567-3570; Colbere-Garapin, F. et al. (1981) J. Mol. Biol. 150:1-14.) Additional selectable genes have been described, e.g., *trpB* and *hisD*, which alter cellular requirements for metabolites. (See, e.g., Hartman, S.C. and R.C. Mulligan (1988) Proc. Natl. Acad. Sci. 85:8047-8051.) Visible markers, e.g., anthocyanins, green fluorescent proteins (GFP; Clontech), β glucuronidase and its substrate β-glucuronide, or luciferase and its substrate luciferin may

be used. These markers can be used not only to identify transformants, but also to quantify the amount of transient or stable protein expression attributable to a specific vector system. (See, e.g., Rhodes, C.A. (1995) Methods Mol. Biol. 55:121-131.)

Although the presence/absence of marker gene expression suggests that the gene of interest is also present, the presence and expression of the gene may need to be confirmed. For example, if the sequence encoding PHSP is inserted within a marker gene sequence, transformed cells containing sequences encoding PHSP can be identified by the absence of marker gene function. Alternatively, a marker gene can be placed in tandem with a sequence encoding PHSP under the control of a single promoter. Expression of the marker gene in response to induction or selection usually indicates expression of the tandem gene as well.

In general, host cells that contain the nucleic acid sequence encoding PHSP and that express PHSP may be identified by a variety of procedures known to those of skill in the art. These procedures include, but are not limited to, DNA-DNA or DNA-RNA hybridizations, PCR amplification, and protein bioassay or immunoassay techniques which include membrane, solution, or chip based technologies for the detection and/or quantification of nucleic acid or protein sequences.

Immunological methods for detecting and measuring the expression of PHSP using either specific polyclonal or monoclonal antibodies are known in the art. Examples of such techniques include enzyme-linked immunosorbent assays (ELISAs), radioimmunoassays (RIAs), and fluorescence activated cell sorting (FACS). A two-site, monoclonal-based immunoassay utilizing monoclonal antibodies reactive to two non-interfering epitopes on PHSP is preferred, but a competitive binding assay may be employed. These and other assays are well known in the art. (See, e.g., Hampton, R. et al. (1990) Serological Methods, a Laboratory Manual, APS Press, St Paul MN, Sect. IV; Coligan, J. E. et al. (1997) Current Protocols in Immunology, Greene Pub. Associates and Wiley-Interscience, New York NY; and Pound, J.D. (1998) Immunochemical Protocols, Humana Press, Totowa NJ).

A wide variety of labels and conjugation techniques are known by those skilled in the art and may be used in various nucleic acid and amino acid assays. Means for producing labeled hybridization or PCR probes for detecting sequences related to polynucleotides encoding PHSP include oligolabeling, nick translation, end-labeling, or PCR amplification using a labeled nucleotide.

30 Alternatively, the sequences encoding PHSP, or any fragments thereof, may be cloned into a vector for the production of an mRNA probe. Such vectors are known in the art, are commercially available, and may be used to synthesize RNA probes in vitro by addition of an appropriate RNA polymerase such as T7, T3, or SP6 and labeled nucleotides. These procedures may be conducted using a variety of commercially available kits, such as those provided by Amersham Pharmacia Biotech, Promega (Madison WI), and US Biochemical. Suitable reporter molecules or labels which may be used for

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ease of detection include radionuclides, enzymes, fluorescent, chemiluminescent, or chromogenic agents, as well as substrates, cofactors, inhibitors, magnetic particles, and the like.

Host cells transformed with nucleotide sequences encoding PHSP may be cultured under conditions suitable for the expression and recovery of the protein from cell culture. The protein produced by a transformed cell may be secreted or retained intracellularly depending on the sequence and/or the vector used. As will be understood by those of skill in the art, expression vectors containing polynucleotides which encode PHSP may be designed to contain signal sequences which direct secretion of PHSP through a prokaryotic or eukaryotic cell membrane.

In addition, a host cell strain may be chosen for its ability to modulate expression of the inserted sequences or to process the expressed protein in the desired fashion. Such modifications of the polypeptide include, but are not limited to, acetylation, carboxylation, glycosylation, phosphorylation, lipidation, and acylation. Post-translational processing which cleaves a "prepro" form of the protein may also be used to specify protein targeting, folding, and/or activity. Different host cells which have specific cellular machinery and characteristic mechanisms for post-translational activities (e.g., CHO, HeLa, MDCK, HEK293, and WI38), are available from the American Type Culture Collection (ATCC, Bethesda MD) and may be chosen to ensure the correct modification and processing of the foreign protein.

In another embodiment of the invention, natural, modified, or recombinant nucleic acid sequences encoding PHSP may be ligated to a heterologous sequence resulting in translation of a 20 fusion protein in any of the aforementioned host systems. For example, a chimeric PHSP protein containing a heterologous moiety that can be recognized by a commercially available antibody may facilitate the screening of peptide libraries for inhibitors of PHSP activity. Heterologous protein and peptide moieties may also facilitate purification of fusion proteins using commercially available affinity matrices. Such moieties include, but are not limited to, glutathione S-transferase (GST), maltose binding protein (MBP), thioredoxin (Trx), calmodulin binding peptide (CBP), 6-His, FLAG, c-myc, and hemagglutinin (HA). GST, MBP, Trx, CBP, and 6-His enable purification of their cognate fusion proteins on immobilized glutathione, maltose, phenylarsine oxide, calmodulin, and metalchelate resins, respectively. FLAG, c-myc, and hemagglutinin (HA) enable immunoaffinity purification of fusion proteins using commercially available monoclonal and polyclonal antibodies 30 that specifically recognize these epitope tags. A fusion protein may also be engineered to contain a proteolytic cleavage site located between the PHSP encoding sequence and the heterologous protein sequence, so that PHSP may be cleaved away from the heterologous moiety following purification. Methods for fusion protein expression and purification are discussed in Ausubel (1995, supra, ch 10). A variety of commercially available kits may also be used to facilitate expression and purification of fusion proteins.

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In a further embodiment of the invention, synthesis of radiolabeled PHSP may be achieved in vitro using the TNT rabbit reticulocyte lysate or wheat germ extract systems (Promega). These systems couple transcription and translation of protein-coding sequences operably associated with the T7, T3, or SP6 promoters. Translation takes place in the presence of a radiolabeled amino acid precursor, preferably <sup>35</sup>S-methionine.

Fragments of PHSP may be produced not only by recombinant production, but also by direct peptide synthesis using solid-phase techniques. (See, e.g., Creighton, supra, pp. 55-60.) Protein synthesis may be performed by manual techniques or by automation. Automated synthesis may be achieved, for example, using the ABI 431A Peptide Synthesizer (Perkin-Elmer). Various fragments 10 of PHSP may be synthesized separately and then combined to produce the full length molecule.

## **THERAPEUTICS**

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Chemical and structural similarity, e.g., in the context of sequences and motifs, exists between regions of PHSP and protein phosphatases. In addition, the expression of PHSP is closely associated with reproductive tissue, nervous tissue, gastrointestinal tissue, cell proliferation, cancer, 15 inflammation, and immune response. Therefore, PHSP appears to play a role in cell proliferative, immune, and neuronal disorders. In the treatment of disorders associated with increased PHSP expression or activity, it is desirable to decrease the expression or activity of PHSP. In the treatment of disorders associated with decreased PHSP expression or activity, it is desirable to increase the expression or activity of PHSP.

Therefore, in one embodiment, PHSP or a fragment or derivative thereof may be administered to a subject to treat or prevent a disorder associated with decreased expression or activity of PHSP. Examples of such disorders include, but are not limited to, a cell proliferative disorder, such as actinic keratosis, arteriosclerosis, atherosclerosis, bursitis, cirrhosis, hepatitis, mixed connective tissue disease (MCTD), myelofibrosis, paroxysmal nocturnal hemoglobinuria, polycythemia vera, psoriasis, primary 25 thrombocythemia, and cancers including adenocarcinoma, leukemia, lymphoma, melanoma, myeloma, sarcoma, teratocarcinoma, and, in particular, cancers of the adrenal gland, bladder, bone, bone marrow, brain, breast, cervix, gall bladder, ganglia, gastrointestinal tract, heart, kidney, liver, lung, muscle, ovary, pancreas, parathyroid, penis, prostate, salivary glands, skin, spleen, testis, thymus, thyroid, and uterus; an immune disorder, such as acquired immunodeficiency syndrome (AIDS), 30 Addison's disease, adult respiratory distress syndrome, allergies, ankylosing spondylitis, amyloidosis, anemia, asthma, atherosclerosis, autoimmune hemolytic anemia, autoimmune thyroiditis, autoimmune polyenodocrinopathy-candidiasis-ectodermal dystrophy (APECED), bronchitis, cholecystitis, contact dermatitis, Crohn's disease, atopic dermatitis, dermatomyositis, diabetes mellitus, emphysema, episodic lymphopenia with lymphocytotoxins, erythroblastosis fetalis, erythema nodosum, atrophic gastritis, glomerulonephritis, Goodpasture's syndrome, gout, Graves' disease, Hashimoto's thyroiditis,

hypereosinophilia, irritable bowel syndrome, multiple sclerosis, myasthenia gravis, myocardial or pericardial inflammation, osteoarthritis, osteoporosis, pancreatitis, polymyositis, psoriasis, Reiter's syndrome, rheumatoid arthritis, scleroderma, Sjögren's syndrome, systemic anaphylaxis, systemic lupus erythematosus, systemic sclerosis, thrombocytopenic purpura, ulcerative colitis, uveitis, Werner syndrome, complications of cancer, hemodialysis, and extracorporeal circulation, viral, bacterial, fungal, parasitic, protozoal, and helminthic infections, and trauma; and a neuronal disorder, such as akathesia, Alzheimer's disease, amnesia, amyotrophic lateral sclerosis, bipolar disorder, catatonia, dementia, depression, diabetic neuropathy, Down's syndrome, tardive dyskinesia, dystonias, epilepsy, Huntington's disease, peripheral neuropathy, multiple sclerosis, neurofibromatosis, Parkinson's disease, paranoid psychoses, postherpetic neuralgia, schizophrenia, and Tourette's disorder.

In another embodiment, a vector capable of expressing PHSP or a fragment or derivative thereof may be administered to a subject to treat or prevent a disorder associated with decreased expression or activity of PHSP including, but not limited to, those described above.

In a further embodiment, a pharmaceutical composition comprising a substantially purified
PHSP in conjunction with a suitable pharmaceutical carrier may be administered to a subject to treat
or prevent a disorder associated with decreased expression or activity of PHSP including, but not
limited to, those provided above.

In still another embodiment, an agonist which modulates the activity of PHSP may be administered to a subject to treat or prevent a disorder associated with decreased expression or activity of PHSP including, but not limited to, those listed above.

In a further embodiment, an antagonist of PHSP may be administered to a subject to treat or prevent a disorder associated with increased expression or activity of PHSP. Examples of such disorders include, but are not limited to, those described above. In one aspect, an antibody which specifically binds PHSP may be used directly as an antagonist or indirectly as a targeting or delivery mechanism for bringing a pharmaceutical agent to cells or tissue which express PHSP.

In an additional embodiment, a vector expressing the complement of the polynucleotide encoding PHSP may be administered to a subject to treat or prevent a disorder associated with increased expression or activity of PHSP including, but not limited to, those described above.

In other embodiments, any of the proteins, antagonists, antibodies, agonists, complementary sequences, or vectors of the invention may be administered in combination with other appropriate therapeutic agents. Selection of the appropriate agents for use in combination therapy may be made by one of ordinary skill in the art, according to conventional pharmaceutical principles. The combination of therapeutic agents may act synergistically to effect the treatment or prevention of the various disorders described above. Using this approach, one may be able to achieve therapeutic efficacy with lower dosages of each agent, thus reducing the potential for adverse side effects.

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An antagonist of PHSP may be produced using methods which are generally known in the art. In particular, purified PHSP may be used to produce antibodies or to screen libraries of pharmaceutical agents to identify those which specifically bind PHSP. Antibodies to PHSP may also be generated using methods that are well known in the art. Such antibodies may include, but are not limited to, polyclonal, monoclonal, chimeric, and single chain antibodies, Fab fragments, and fragments produced by a Fab expression library. Neutralizing antibodies (i.e., those which inhibit dimer formation) are especially preferred for therapeutic use.

For the production of antibodies, various hosts including goats, rabbits, rats, mice, humans, and others may be immunized by injection with PHSP or with any fragment or oligopeptide thereof which has immunogenic properties. Depending on the host species, various adjuvants may be used to increase immunological response. Such adjuvants include, but are not limited to, Freund's, mineral gels such as aluminum hydroxide, and surface active substances such as lysolecithin, pluronic polyols, polyanions, peptides, oil emulsions, KLH, and dinitrophenol. Among adjuvants used in humans, BCG (bacilli Calmette-Guerin) and Corynebacterium parvum are especially preferable.

It is preferred that the oligopeptides, peptides, or fragments used to induce antibodies to PHSP have an amino acid sequence consisting of at least about 5 amino acids, and, more preferably, of at least about 10 amino acids. It is also preferable that these oligopeptides, peptides, or fragments are identical to a portion of the amino acid sequence of the natural protein and contain the entire amino acid sequence of a small, naturally occurring molecule. Short stretches of PHSP amino acids may be fused with those of another protein, such as KLH, and antibodies to the chimeric molecule may be produced.

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Monoclonal antibodies to PHSP may be prepared using any technique which provides for the production of antibody molecules by continuous cell lines in culture. These include, but are not limited to, the hybridoma technique, the human B-cell hybridoma technique, and the EBV-hybridoma technique. (See, e.g., Kohler, G. et al. (1975) Nature 256:495-497; Kozbor, D. et al. (1985) J. Immunol. Methods 81:31-42; Cote, R.J. et al. (1983) Proc. Natl. Acad. Sci. 80:2026-2030; and Cole, S.P. et al. (1984) Mol. Cell Biol. 62:109-120.)

In addition, techniques developed for the production of "chimeric antibodies," such as the splicing of mouse antibody genes to human antibody genes to obtain a molecule with appropriate antigen specificity and biological activity, can be used. (See, e.g., Morrison, S.L. et al. (1984) Proc. Natl. Acad. Sci. 81:6851-6855; Neuberger, M.S. et al. (1984) Nature 312:604-608; and Takeda, S. et al. (1985) Nature 314:452-454.) Alternatively, techniques described for the production of single chain antibodies may be adapted, using methods known in the art, to produce PHSP-specific single chain antibodies. Antibodies with related specificity, but of distinct idiotypic composition, may be generated by chain shuffling from random combinatorial immunoglobulin libraries. (See, e.g., Burton

D.R. (1991) Proc. Natl. Acad. Sci. 88:10134-10137.)

Antibodies may also be produced by inducing <u>in vivo</u> production in the lymphocyte population or by screening immunoglobulin libraries or panels of highly specific binding reagents as disclosed in the literature. (See, e.g., Orlandi, R. et al. (1989) Proc. Natl. Acad. Sci. 86: 3833-3837; Winter, G. et al. (1991) Nature 349:293-299.)

Antibody fragments which contain specific binding sites for PHSP may also be generated. For example, such fragments include, but are not limited to, F(ab')2 fragments produced by pepsin digestion of the antibody molecule and Fab fragments generated by reducing the disulfide bridges of the F(ab')2 fragments. Alternatively, Fab expression libraries may be constructed to allow rapid and easy identification of monoclonal Fab fragments with the desired specificity. (See, e.g., Huse, W.D. et al. (1989) Science 246:1275-1281.)

Various immunoassays may be used for screening to identify antibodies having the desired specificity. Numerous protocols for competitive binding or immunoradiometric assays using either polyclonal or monoclonal antibodies with established specificities are well known in the art. Such immunoassays typically involve the measurement of complex formation between PHSP and its specific antibody. A two-site, monoclonal-based immunoassay utilizing monoclonal antibodies reactive to two non-interfering PHSP epitopes is preferred, but a competitive binding assay may also be employed (Pound, supra).

Various methods such as Scatchard analysis in conjunction with radioimmunoassay techniques may be used to assess the affinity of antibodies for PHSP. Affinity is expressed as an association constant, K<sub>a</sub>, which is defined as the molar concentration of PHSP-antibody complex divided by the molar concentrations of free antigen and free antibody under equilibrium conditions. The K<sub>a</sub> determined for a preparation of polyclonal antibodies, which are heterogeneous in their affinities for multiple PHSP epitopes, represents the average affinity, or avidity, of the antibodies for PHSP. The K<sub>a</sub> determined for a preparation of monoclonal antibodies, which are monospecific for a particular PHSP epitope, represents a true measure of affinity. High-affinity antibody preparations with K<sub>a</sub> ranging from about 10° to 10¹² L/mole are preferred for use in immunoassays in which the PHSP-antibody complex must withstand rigorous manipulations. Low-affinity antibody preparations with K<sub>a</sub> ranging from about 10° to 10¹ L/mole are preferred for use in immunopurification and similar procedures which ultimately require dissociation of PHSP, preferably in active form, from the antibody (Catty, D. (1988) Antibodies, Volume I: A Practical Approach, IRL Press, Washington, DC; Liddell, J. E. and Cryer, A. (1991) A Practical Guide to Monoclonal Antibodies, John Wiley & Sons, New York NY).

The titer and avidity of polyclonal antibody preparations may be further evaluated to determine the quality and suitability of such preparations for certain downstream applications. For

example, a polyclonal antibody preparation containing at least 1-2 mg specific antibody/ml, preferably 5-10 mg specific antibody/ml, is preferred for use in procedures requiring precipitation of PHSP-antibody complexes. Procedures for evaluating antibody specificity, titer, and avidity, and guidelines for antibody quality and usage in various applications, are generally available. (See, e.g., Catty, <u>supra</u>, and Coligan et al. <u>supra</u>.)

In another embodiment of the invention, the polynucleotides encoding PHSP, or any fragment or complement thereof, may be used for therapeutic purposes. In one aspect, the complement of the polynucleotide encoding PHSP may be used in situations in which it would be desirable to block the transcription of the mRNA. In particular, cells may be transformed with sequences complementary to polynucleotides encoding PHSP. Thus, complementary molecules or fragments may be used to modulate PHSP activity, or to achieve regulation of gene function. Such technology is now well known in the art, and sense or antisense oligonucleotides or larger fragments can be designed from various locations along the coding or control regions of sequences encoding PHSP.

Expression vectors derived from retroviruses, adenoviruses, or herpes or vaccinia viruses, or from various bacterial plasmids, may be used for delivery of nucleotide sequences to the targeted organ, tissue, or cell population. Methods which are well known to those skilled in the art can be used to construct vectors to express nucleic acid sequences complementary to the polynucleotides encoding PHSP. (See, e.g., Sambrook, <u>supra</u>; Ausubel, 1995, <u>supra</u>.)

Genes encoding PHSP can be turned off by transforming a cell or tissue with expression vectors which express high levels of a polynucleotide, or fragment thereof, encoding PHSP. Such constructs may be used to introduce untranslatable sense or antisense sequences into a cell. Even in the absence of integration into the DNA, such vectors may continue to transcribe RNA molecules until they are disabled by endogenous nucleases. Transient expression may last for a month or more with a non-replicating vector, and may last even longer if appropriate replication elements are part of the vector system.

As mentioned above, modifications of gene expression can be obtained by designing complementary sequences or antisense molecules (DNA, RNA, or PNA) to the control, 5', or regulatory regions of the gene encoding PHSP. Oligonucleotides derived from the transcription initiation site, e.g., between about positions -10 and +10 from the start site, are preferred. Similarly, inhibition can be achieved using triple helix base-pairing methodology. Triple helix pairing is useful because it causes inhibition of the ability of the double helix to open sufficiently for the binding of polymerases, transcription factors, or regulatory molecules. Recent therapeutic advances using triplex DNA have been described in the literature. (See, e.g., Gee, J.E. et al. (1994) in Huber, B.E. and B.I. Carr, Molecular and Immunologic Approaches, Futura Publishing, Mt. Kisco NY, pp. 163-177.) A complementary sequence or antisense molecule may also be designed to block translation of mRNA

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by preventing the transcript from binding to ribosomes.

Ribozymes, enzymatic RNA molecules, may also be used to catalyze the specific cleavage of RNA. The mechanism of ribozyme action involves sequence-specific hybridization of the ribozyme molecule to complementary target RNA, followed by endonucleolytic cleavage. For example, engineered hammerhead motif ribozyme molecules may specifically and efficiently catalyze endonucleolytic cleavage of sequences encoding PHSP.

Specific ribozyme cleavage sites within any potential RNA target are initially identified by scanning the target molecule for ribozyme cleavage sites, including the following sequences: GUA, GUU, and GUC. Once identified, short RNA sequences of between 15 and 20 ribonucleotides, corresponding to the region of the target gene containing the cleavage site, may be evaluated for secondary structural features which may render the oligonucleotide inoperable. The suitability of candidate targets may also be evaluated by testing accessibility to hybridization with complementary oligonucleotides using ribonuclease protection assays.

Complementary ribonucleic acid molecules and ribozymes of the invention may be prepared by any method known in the art for the synthesis of nucleic acid molecules. These include techniques for chemically synthesizing oligonucleotides such as solid phase phosphoramidite chemical synthesis. Alternatively, RNA molecules may be generated by in vitro and in vivo transcription of DNA sequences encoding PHSP. Such DNA sequences may be incorporated into a wide variety of vectors with suitable RNA polymerase promoters such as T7 or SP6. Alternatively, these cDNA constructs that synthesize complementary RNA, constitutively or inducibly, can be introduced into cell lines, cells, or tissues.

RNA molecules may be modified to increase intracellular stability and half-life. Possible modifications include, but are not limited to, the addition of flanking sequences at the 5' and/or 3' ends of the molecule, or the use of phosphorothioate or 2' O-methyl rather than phosphodiesterase linkages within the backbone of the molecule. This concept is inherent in the production of PNAs and can be extended in all of these molecules by the inclusion of nontraditional bases such as inosine, queosine, and wybutosine, as well as acetyl-, methyl-, thio-, and similarly modified forms of adenine, cytidine, guanine, thymine, and uridine which are not as easily recognized by endogenous endonucleases.

Many methods for introducing vectors into cells or tissues are available and equally suitable for use in vivo, in vitro, and ex vivo. For ex vivo therapy, vectors may be introduced into stem cells taken from the patient and clonally propagated for autologous transplant back into that same patient. Delivery by transfection, by liposome injections, or by polycationic amino polymers may be achieved using methods which are well known in the art. (See, e.g., Goldman, C.K. et al. (1997) Nature Biotechnology 15:462-466.)

35 Any of the therapeutic methods described above may be applied to any subject in need of such

therapy, including, for example, mammals such as dogs, cats, cows, horses, rabbits, monkeys, and most preferably, humans.

An additional embodiment of the invention relates to the administration of a pharmaceutical or sterile composition, in conjunction with a pharmaceutically acceptable carrier, for any of the therapeutic effects discussed above. Such pharmaceutical compositions may consist of PHSP, antibodies to PHSP, and mimetics, agonists, antagonists, or inhibitors of PHSP. The compositions may be administered alone or in combination with at least one other agent, such as a stabilizing compound, which may be administered in any sterile, biocompatible pharmaceutical carrier including, but not limited to, saline, buffered saline, dextrose, and water. The compositions may be administered to a patient alone, or in combination with other agents, drugs, or hormones.

The pharmaceutical compositions utilized in this invention may be administered by any number of routes including, but not limited to, oral, intravenous, intramuscular, intra-arterial, intramedullary, intrathecal, intraventricular, transdermal, subcutaneous, intraperitoneal, intranasal, enteral, topical, sublingual, or rectal means.

In addition to the active ingredients, these pharmaceutical compositions may contain suitable pharmaceutically-acceptable carriers comprising excipients and auxiliaries which facilitate processing of the active compounds into preparations which can be used pharmaceutically. Further details on techniques for formulation and administration may be found in the latest edition of <u>Remington's Pharmaceutical Sciences</u> (Maack Publishing, Easton PA).

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Pharmaceutical compositions for oral administration can be formulated using pharmaceutically acceptable carriers well known in the art in dosages suitable for oral administration. Such carriers enable the pharmaceutical compositions to be formulated as tablets, pills, dragees, capsules, liquids, gels, syrups, slurries, suspensions, and the like, for ingestion by the patient.

Pharmaceutical preparations for oral use can be obtained through combining active compounds with solid excipient and processing the resultant mixture of granules (optionally, after grinding) to obtain tablets or dragee cores. Suitable auxiliaries can be added, if desired. Suitable excipients include carbohydrate or protein fillers, such as sugars, including lactose, sucrose, mannitol, and sorbitol; starch from corn, wheat, rice, potato, or other plants; cellulose, such as methyl cellulose, hydroxypropylmethyl-cellulose, or sodium carboxymethylcellulose; gums, including arabic and tragacanth; and proteins, such as gelatin and collagen. If desired, disintegrating or solubilizing agents may be added, such as the cross-linked polyvinyl pyrrolidone, agar, and alginic acid or a salt thereof, such as sodium alginate.

Dragee cores may be used in conjunction with suitable coatings, such as concentrated sugar solutions, which may also contain gum arabic, tale, polyvinylpyrrolidone, carbopol gel, polyethylene glycol, and/or titanium dioxide, lacquer solutions, and suitable organic solvents or solvent mixtures.

Dyestuffs or pigments may be added to the tablets or dragee coatings for product identification or to characterize the quantity of active compound, i.e., dosage.

Pharmaceutical preparations which can be used orally include push-fit capsules made of gelatin, as well as soft, sealed capsules made of gelatin and a coating, such as glycerol or sorbitol.

Push-fit capsules can contain active ingredients mixed with fillers or binders, such as lactose or starches, lubricants, such as talc or magnesium stearate, and, optionally, stabilizers. In soft capsules, the active compounds may be dissolved or suspended in suitable liquids, such as fatty oils, liquid, or liquid polyethylene glycol with or without stabilizers.

Pharmaceutical formulations suitable for parenteral administration may be formulated in aqueous solutions, preferably in physiologically compatible buffers such as Hanks' solution, Ringer's solution, or physiologically buffered saline. Aqueous injection suspensions may contain substances which increase the viscosity of the suspension, such as sodium carboxymethyl cellulose, sorbitol, or dextran. Additionally, suspensions of the active compounds may be prepared as appropriate oily injection suspensions. Suitable lipophilic solvents or vehicles include fatty oils, such as sesame oil, or synthetic fatty acid esters, such as ethyl oleate, triglycerides, or liposomes. Non-lipid polycationic amino polymers may also be used for delivery. Optionally, the suspension may also contain suitable stabilizers or agents to increase the solubility of the compounds and allow for the preparation of highly concentrated solutions.

For topical or nasal administration, penetrants appropriate to the particular barrier to be permeated are used in the formulation. Such penetrants are generally known in the art.

The pharmaceutical compositions of the present invention may be manufactured in a manner that is known in the art, e.g., by means of conventional mixing, dissolving, granulating, dragee-making, levigating, emulsifying, encapsulating, entrapping, or lyophilizing processes.

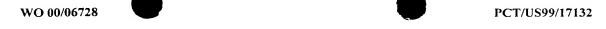
The pharmaceutical composition may be provided as a salt and can be formed with many acids, including but not limited to, hydrochloric, sulfuric, acetic, lactic, tartaric, malic, and succinic acid. Salts tend to be more soluble in aqueous or other protonic solvents than are the corresponding free base forms. In other cases, the preferred preparation may be a lyophilized powder which may contain any or all of the following: 1 mM to 50 mM histidine, 0.1% to 2% sucrose, and 2% to 7% mannitol, at a pH range of 4.5 to 5.5, that is combined with buffer prior to use.

After pharmaceutical compositions have been prepared, they can be placed in an appropriate container and labeled for treatment of an indicated condition. For administration of PHSP, such labeling would include amount, frequency, and method of administration.

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Pharmaceutical compositions suitable for use in the invention include compositions wherein the active ingredients are contained in an effective amount to achieve the intended purpose. The determination of an effective dose is well within the capability of those skilled in the art.



For any compound, the therapeutically effective dose can be estimated initially either in cell culture assays, e.g., of neoplastic cells or in animal models such as mice, rats, rabbits, dogs, or pigs. An animal model may also be used to determine the appropriate concentration range and route of administration. Such information can then be used to determine useful doses and routes for administration in humans.

A therapeutically effective dose refers to that amount of active ingredient, for example PHSP or fragments thereof, antibodies of PHSP, and agonists, antagonists or inhibitors of PHSP, which ameliorates the symptoms or condition. Therapeutic efficacy and toxicity may be determined by standard pharmaceutical procedures in cell cultures or with experimental animals, such as by calculating the ED<sub>50</sub> (the dose therapeutically effective in 50% of the population) or LD<sub>50</sub> (the dose lethal to 50% of the population) statistics. The dose ratio of toxic to therapeutic effects is the therapeutic index, which can be expressed as the LD<sub>50</sub>/ED<sub>50</sub> ratio. Pharmaceutical compositions which exhibit large therapeutic indices are preferred. The data obtained from cell culture assays and animal studies are used to formulate a range of dosage for human use. The dosage contained in such compositions is preferably within a range of circulating concentrations that includes the ED<sub>50</sub> with little or no toxicity. The dosage varies within this range depending upon the dosage form employed, the sensitivity of the patient, and the route of administration.

The exact dosage will be determined by the practitioner, in light of factors related to the subject requiring treatment. Dosage and administration are adjusted to provide sufficient levels of the active moiety or to maintain the desired effect. Factors which may be taken into account include the severity of the disease state, the general health of the subject, the age, weight, and gender of the subject, time and frequency of administration, drug combination(s), reaction sensitivities, and response to therapy. Long-acting pharmaceutical compositions may be administered every 3 to 4 days, every week, or biweekly depending on the half-life and clearance rate of the particular formulation.

Normal dosage amounts may vary from about  $0.1~\mu g$  to  $100,000~\mu g$ , up to a total dose of about 1 gram, depending upon the route of administration. Guidance as to particular dosages and methods of delivery is provided in the literature and generally available to practitioners in the art. Those skilled in the art will employ different formulations for nucleotides than for proteins or their inhibitors. Similarly, delivery of polynucleotides or polypeptides will be specific to particular cells, conditions, locations, etc.

# **DIAGNOSTICS**

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In another embodiment, antibodies which specifically bind PHSP may be used for the diagnosis of disorders characterized by expression of PHSP, or in assays to monitor patients being treated with PHSP or agonists, antagonists, or inhibitors of PHSP. Antibodies useful for diagnostic

purposes may be prepared in the same manner as described above for therapeutics. Diagnostic assays for PHSP include methods which utilize the antibody and a label to detect PHSP in human body fluids or in extracts of cells or tissues. The antibodies may be used with or without modification, and may be labeled by covalent or non-covalent attachment of a reporter molecule. A wide variety of reporter molecules, several of which are described above, are known in the art and may be used.

A variety of protocols for measuring PHSP, including ELISAs, RIAs, and FACS, are known in the art and provide a basis for diagnosing altered or abnormal levels of PHSP expression. Normal or standard values for PHSP expression are established by combining body fluids or cell extracts taken  $from \, normal \, mammalian \, subjects, \, preferably \, human, \, with \, antibody \, to \, PHSP \, under \, conditions \, suitable \, and \, the subjects \, are the subjects and \, the subjects \, are the subjects and \, the subjects \, are the subjects \, and \, the subjects \, are the subject \,$ for complex formation. The amount of standard complex formation may be quantitated by various methods, preferably by photometric means. Quantities of PHSP expressed in subject, control, and disease samples from biopsied tissues are compared with the standard values. Deviation between standard and subject values establishes the parameters for diagnosing disease.

In another embodiment of the invention, the polynucleotides encoding PHSP may be used for diagnostic purposes. The polynucleotides which may be used include oligonucleotide sequences, complementary RNA and DNA molecules, and PNAs. The polynucleotides may be used to detect and quantitate gene expression in biopsied tissues in which expression of PHSP may be correlated with disease. The diagnostic assay may be used to determine absence, presence, and excess expression of PHSP, and to monitor regulation of PHSP levels during therapeutic intervention.

In one aspect, hybridization with PCR probes which are capable of detecting polynucleotide sequences, including genomic sequences, encoding PHSP or closely related molecules may be used to identify nucleic acid sequences which encode PHSP. The specificity of the probe, whether it is made from a highly specific region, e.g., the 5' regulatory region, or from a less specific region, e.g., a conserved motif, and the stringency of the hybridization or amplification (maximal, high, 25 intermediate, or low), will determine whether the probe identifies only naturally occurring sequences encoding PHSP, allelic variants, or related sequences.

Probes may also be used for the detection of related sequences, and should preferably have at least 50% sequence identity to any of the PHSP encoding sequences. The hybridization probes of the subject invention may be DNA or RNA and may be derived from the sequence of SEQ ID NO:32-62 or from genomic sequences including promoters, enhancers, and introns of the PHSP gene.

Means for producing specific hybridization probes for DNAs encoding PHSP include the cloning of polynucleotide sequences encoding PHSP or PHSP derivatives into vectors for the production of mRNA probes. Such vectors are known in the art, are commercially available, and may be used to synthesize RNA probes in vitro by means of the addition of the appropriate RNA polymerases and the appropriate labeled nucleotides. Hybridization probes may be labeled by a

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variety of reporter groups, for example, by radionuclides such as <sup>32</sup>P or <sup>35</sup>S, or by enzymatic labels, such as alkaline phosphatase coupled to the probe via avidin/biotin coupling systems, and the like.

Polynucleotide sequences encoding PHSP may be used for the diagnosis of disorders associated with expression of PHSP. Examples of such disorders include, but are not limited to, a cell proliferative disorder, such as actinic keratosis, arteriosclerosis, atherosclerosis, bursitis, cirrhosis, hepatitis, mixed connective tissue disease (MCTD), myelofibrosis, paroxysmal nocturnal hemoglobinuria, polycythemia vera, psoriasis, primary thrombocythemia, and cancers including adenocarcinoma, leukemia, lymphoma, melanoma, myeloma, sarcoma, teratocarcinoma, and, in particular, cancers of the adrenal gland, bladder, bone, bone marrow, brain, breast, cervix, gall bladder, ganglia, gastrointestinal tract, heart, kidney, liver, lung, muscle, ovary, pancreas, parathyroid, penis, prostate, salivary glands, skin, spleen, testis, thymus, thyroid, and uterus; an immune disorder, such as acquired immunodeficiency syndrome (AIDS), Addison's disease, adult respiratory distress syndrome, allergies, ankylosing spondylitis, amyloidosis, anemia, asthma, atherosclerosis, autoimmune hemolytic anemia, autoimmune thyroiditis, autoimmune polyenodocrinopathy-15 candidiasis-ectodermal dystrophy (APECED), bronchitis, cholecystitis, contact dermatitis, Crohn's disease, atopic dermatitis, dermatomyositis, diabetes mellitus, emphysema, episodic lymphopenia with lymphocytotoxins, erythroblastosis fetalis, erythema nodosum, atrophic gastritis, glomerulonephritis, Goodpasture's syndrome, gout, Graves' disease, Hashimoto's thyroiditis, hypereosinophilia, irritable bowel syndrome, multiple sclerosis, myasthenia gravis, myocardial or pericardial inflammation, osteoarthritis, osteoporosis, pancreatitis, polymyositis, psoriasis, Reiter's syndrome, rheumatoid arthritis, scleroderma, Sjögren's syndrome, systemic anaphylaxis, systemic lupus erythematosus, systemic sclerosis, thrombocytopenic purpura, ulcerative colitis, uveitis, Werner syndrome, complications of cancer, hemodialysis, and extracorporeal circulation, viral, bacterial, fungal, parasitic, protozoal, and helminthic infections, and trauma; and a neuronal disorder, such as akathesia, Alzheimer's disease, amnesia, amyotrophic lateral sclerosis, bipolar disorder, catatonia, dementia, depression, diabetic neuropathy, Down's syndrome, tardive dyskinesia, dystonias, epilepsy, Huntington's disease, peripheral neuropathy, multiple sclerosis, neurofibromatosis, Parkinson's disease, paranoid psychoses, postherpetic neuralgia, schizophrenia, and Tourette's disorder. The polynucleotide sequences encoding PHSP may be used in Southern or northern analysis, dot blot, or other membrane-based technologies; in PCR technologies; in dipstick, pin, and multiformat ELISAlike assays; and in microarrays utilizing fluids or tissues from patients to detect altered PHSP expression. Such qualitative or quantitative methods are well known in the art.

In a particular aspect, the nucleotide sequences encoding PHSP may be useful in assays that detect the presence of associated disorders, particularly those mentioned above. The nucleotide sequences encoding PHSP may be labeled by standard methods and added to a fluid or tissue sample

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from a patient under conditions suitable for the formation of hybridization complexes. After a suitable incubation period, the sample is washed and the signal is quantitated and compared with a standard value. If the amount of signal in the patient sample is significantly altered in comparison to a control sample then the presence of altered levels of nucleotide sequences encoding PHSP in the sample indicates the presence of the associated disorder. Such assays may also be used to evaluate the efficacy of a particular therapeutic treatment regimen in animal studies, in clinical trials, or to monitor the treatment of an individual patient.

In order to provide a basis for the diagnosis of a disorder associated with expression of PHSP, a normal or standard profile for expression is established. This may be accomplished by combining body fluids or cell extracts taken from normal subjects, either animal or human, with a sequence, or a fragment thereof, encoding PHSP, under conditions suitable for hybridization or amplification. Standard hybridization may be quantified by comparing the values obtained from normal subjects with values from an experiment in which a known amount of a substantially purified polynucleotide is used. Standard values obtained in this manner may be compared with values obtained from samples from patients who are symptomatic for a disorder. Deviation from standard values is used to establish the presence of a disorder.

Once the presence of a disorder is established and a treatment protocol is initiated, hybridization assays may be repeated on a regular basis to determine if the level of expression in the patient begins to approximate that which is observed in the normal subject. The results obtained from successive assays may be used to show the efficacy of treatment over a period ranging from several days to months.

With respect to cancer, the presence of an abnormal amount of transcript (either under- or overexpressed) in biopsied tissue from an individual may indicate a predisposition for the development of the disease, or may provide a means for detecting the disease prior to the appearance of actual clinical symptoms. A more definitive diagnosis of this type may allow health professionals to employ preventative measures or aggressive treatment earlier thereby preventing the development or further progression of the cancer.

Additional diagnostic uses for oligonucleotides designed from the sequences encoding PHSP may involve the use of PCR. These oligomers may be chemically synthesized, generated enzymatically, or produced in vitro. Oligomers will preferably contain a fragment of a polynucleotide encoding PHSP, or a fragment of a polynucleotide complementary to the polynucleotide encoding PHSP, and will be employed under optimized conditions for identification of a specific gene or condition. Oligomers may also be employed under less stringent conditions for detection or quantitation of closely related DNA or RNA sequences.

Methods which may also be used to quantify the expression of PHSP include radiolabeling

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or biotinylating nucleotides, coamplification of a control nucleic acid, and interpolating results from standard curves. (See, e.g., Melby, P.C. et al. (1993) J. Immunol. Methods 159:235-244; Duplaa, C. et al. (1993) Anal. Biochem. 212:229-236.) The speed of quantitation of multiple samples may be accelerated by running the assay in an ELISA format where the oligomer of interest is presented in various dilutions and a spectrophotometric or colorimetric response gives rapid quantitation.

In further embodiments, oligonucleotides or longer fragments derived from any of the polynucleotide sequences described herein may be used as targets in a microarray. The microarray can be used to monitor the expression level of large numbers of genes simultaneously and to identify genetic variants, mutations, and polymorphisms. This information may be used to determine gene function, to understand the genetic basis of a disorder, to diagnose a disorder, and to develop and monitor the activities of therapeutic agents.

Microarrays may be prepared, used, and analyzed using methods known in the art. (See, e.g., Brennan, T.M. et al. (1995) U.S. Patent No. 5,474,796; Schena, M. et al. (1996) Proc. Natl. Acad. Sci. 93:10614-10619; Baldeschweiler et al. (1995) PCT application WO95/251116; Shalon, D. et al. (1995) PCT application WO95/35505; Heller, R.A. et al. (1997) Proc. Natl. Acad. Sci. 94:2150-2155; and Heller, M.J. et al. (1997) U.S. Patent No. 5,605,662.)

In another embodiment of the invention, nucleic acid sequences encoding PHSP may be used to generate hybridization probes useful in mapping the naturally occurring genomic sequence. The sequences may be mapped to a particular chromosome, to a specific region of a chromosome, or to artificial chromosome constructions, e.g., human artificial chromosomes (HACs), yeast artificial chromosomes (YACs), bacterial artificial chromosomes (BACs), bacterial P1 constructions, or single chromosome cDNA libraries. (See, e.g., Harrington, J.J. et al. (1997) Nat Genet. 15:345-355; Price, C.M. (1993) Blood Rev. 7:127-134; and Trask, B.J. (1991) Trends Genet. 7:149-154.)

Fluorescent <u>in situ</u> hybridization (FISH) may be correlated with other physical chromosome mapping techniques and genetic map data. (See, e.g., Heinz-Ulrich, et al. (1995) in Meyers, <u>supra</u>, pp. 965-968.) Examples of genetic map data can be found in various scientific journals or at the Online Mendelian Inheritance in Man (OMIM) site. Correlation between the location of the gene encoding PHSP on a physical chromosomal map and a specific disorder, or a predisposition to a specific disorder, may help define the region of DNA associated with that disorder. The nucleotide sequences of the invention may be used to detect differences in gene sequences among normal, carrier, and affected individuals.

In situ hybridization of chromosomal preparations and physical mapping techniques, such as linkage analysis using established chromosomal markers, may be used for extending genetic maps. Often the placement of a gene on the chromosome of another mammalian species, such as mouse, may reveal associated markers even if the number or arm of a particular human chromosome is not known.

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New sequences can be assigned to chromosomal arms by physical mapping. This provides valuable information to investigators searching for disease genes using positional cloning or other gene discovery techniques. Once the disease or syndrome has been crudely localized by genetic linkage to a particular genomic region, e.g., ataxia-telangiectasia to 11q22-23, any sequences mapping to that area may represent associated or regulatory genes for further investigation. (See, e.g., Gatti, R.A. et al. (1988) Nature 336:577-580.) The nucleotide sequence of the subject invention may also be used to detect differences in the chromosomal location due to translocation, inversion, etc., among normal, carrier, or affected individuals.

In another embodiment of the invention, PHSP, its catalytic or immunogenic fragments, or oligopeptides thereof can be used for screening libraries of compounds in any of a variety of drug screening techniques. The fragment employed in such screening may be free in solution, affixed to a solid support, borne on a cell surface, or located intracellularly. The formation of binding complexes between PHSP and the agent being tested may be measured.

Another technique for drug screening provides for high throughput screening of compounds having suitable binding affinity to the protein of interest. (See, e.g., Geysen, et al. (1984) PCT application WO84/03564.) In this method, large numbers of different small test compounds are synthesized on a solid substrate. The test compounds are reacted with PHSP, or fragments thereof, and washed. Bound PHSP is then detected by methods well known in the art. Purified PHSP can also be coated directly onto plates for use in the aforementioned drug screening techniques. Alternatively, non-neutralizing antibodies can be used to capture the peptide and immobilize it on a solid support.

In another embodiment, one may use competitive drug screening assays in which neutralizing antibodies capable of binding PHSP specifically compete with a test compound for binding PHSP. In this manner, antibodies can be used to detect the presence of any peptide which shares one or more antigenic determinants with PHSP.

In additional embodiments, the nucleotide sequences which encode PHSP may be used in any molecular biology techniques that have yet to be developed, provided the new techniques rely on properties of nucleotide sequences that are currently known, including, but not limited to, such properties as the triplet genetic code and specific base pair interactions.

Without further elaboration, it is believed that one skilled in the art can, using the preceding description, utilize the present invention to its fullest extent. The following preferred specific embodiments are, therefore, to be construed as merely illustrative, and not limitative of the remainder of the disclosure in any way whatsoever.

The disclosures of all patents, applications, and publications mentioned above and below, in particular U.S. Ser. No. 09/173,482, 09/123,494, 09/152,814, 09/229,005, 60/106,889, 60/109,093, and 60/113,796, are hereby expressly incorporated by reference.

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### **EXAMPLES**

### I. Construction of cDNA Libraries

RNA was purchased from Clontech or isolated from tissues described in Table 4. Some tissues were homogenized and lysed in guanidinium isothiocyanate, while others were homogenized and lysed in phenol or in a suitable mixture of denaturants, such as TRIZOL (Life Technologies), a monophasic solution of phenol and guanidine isothiocyanate. The resulting lysates were centrifuged over CsCl cushions or extracted with chloroform. RNA was precipitated from the lysates with either isopropanol or sodium acetate and ethanol, or by other routine methods.

Phenol extraction and precipitation of RNA were repeated as necessary to increase RNA purity. In some cases, RNA was treated with DNase. For most libraries, poly(A+) RNA was isolated using oligo d(T)-coupled paramagnetic particles (Promega), OLIGOTEX latex particles (OIAGEN, Chatsworth CA), or an OLIGOTEX mRNA purification kit (QIAGEN). Alternatively, RNA was isolated directly from tissue lysates using other RNA isolation kits, e.g., the POLY(A)PURE mRNA 15 purification kit (Ambion, Austin TX).

In some cases, Stratagene was provided with RNA and constructed the corresponding cDNA libraries. Otherwise, cDNA was synthesized and cDNA libraries were constructed with the UNIZAP vector system (Stratagene) or SUPERSCRIPT plasmid system (Life Technologies), using the recommended procedures or similar methods known in the art. (See, e.g., Ausubel, 1997, supra, units 20 5.1-6.6). Reverse transcription was initiated using oligo d(T) or random primers. Synthetic oligonucleotide adapters were ligated to double stranded cDNA, and the cDNA was digested with the appropriate restriction enzyme or enzymes. For most libraries, the cDNA was size-selected (300-1000 bp) using SEPHACRYL S1000, SEPHAROSE CL2B, or SEPHAROSE CL4B column chromatography (Amersham Pharmacia Biotech) or preparative agarose gel electrophoresis. cDNAs 25 were ligated into compatible restriction enzyme sites of the polylinker of a suitable plasmid, e.g., PBLUESCRIPT plasmid (Stratagene), pSPORT1 plasmid (Life Technologies), or pINCY (Incyte Pharmaceuticals, Palo Alto CA). Recombinant plasmids were transformed into competent E. coli cells including XL1-BLUE, XL1-BLUEMRF, or SOLR from Stratagene or DH5α, DH10B, or ELECTROMAX DH10B from Life Technologies.

### 30 II. Isolation of cDNA Clones

Plasmids were recovered from host cells by in vivo excision, using the UNIZAP vector system (Stratagene) or cell lysis. Plasmids were purified using at least one of the following: a Magic or WIZARD Minipreps DNA purification system (Promega); an AGTC Miniprep purification kit (Edge Biosystems, Gaithersburg MD); and QIAWELL 8 Plasmid, QIAWELL 8 Plus Plasmid, 35 QIAWELL 8 Ultra Plasmid purification systems or the R.E.A.L. PREP 96 plasmid kit from QIAGEN.

Following precipitation, plasmids were resuspended in 0.1 ml of distilled water and stored, with or without lyophilization, at 4°C.

Alternatively, plasmid DNA was amplified from host cell lysates using direct link PCR in a high-throughput format (Rao, V.B. (1994) Anal. Biochem. 216:1-14). Host cell lysis and thermal 5 cycling steps were carried out in a single reaction mixture. Samples were processed and stored in 384-well plates, and the concentration of amplified plasmid DNA was quantified fluorometrically using PICOGREEN dye (Molecular Probes, Eugene OR) and a Fluoroskan II fluorescence scanner (Labsystems Oy, Helsinki, Finland).

### III. Sequencing and Analysis

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cDNA sequencing reactions were processed using standard methods or high-throughput instrumentation such as the ABI CATALYST 800 (Perkin-Elmer) thermal cycler or the PTC-200 thermal cycler (MJ Research) in conjunction with the HYDRA microdispenser (Robbins Scientific) or the MICROLAB 2200 (Hamilton) liquid transfer system. cDNA sequencing reactions were prepared using reagents provided by Amersham Pharmacia Biotech or supplied in ABI sequencing 15 kits such as the ABI PRISM BIGDYE Terminator cycle sequencing ready reaction kit (Perkin-Elmer). Electrophoretic separation of cDNA sequencing reactions and detection of labeled polynucleotides were carried out using the MEGABACE 1000 DNA sequencing system (Molecular Dynamics); the ABI PRISM 373 or 377 sequencing systems (Perkin-Elmer) in conjunction with standard ABI protocols and base calling software; or other sequence analysis systems known in the art. Reading 20 frames within the cDNA sequences were identified using standard methods (reviewed in Ausubel, 1997, supra, unit 7.7). Some of the cDNA sequences were selected for extension using the techniques disclosed in Example V.

The polynucleotide sequences derived from cDNA sequencing were assembled and analyzed using a combination of software programs which utilize algorithms well known to those skilled in the art. Table 5 summarizes the tools, programs, and algorithms used and provides applicable descriptions, references, and threshold parameters. The first column of Table 5 shows the tools, programs, and algorithms used, the second column provides brief descriptions thereof, the third column presents appropriate references, all of which are incorporated by reference herein in their entirety, and the fourth column presents, where applicable, the scores, probability values, and other 30 parameters used to evaluate the strength of a match between two sequences (the higher the score, the greater the homology between two sequences). Sequences were analyzed using MACDNASIS PRO software (Hitachi Software Engineering, South San Francisco CA) and LASERGENE software (DNASTAR).

The polynucleotide sequences were validated by removing vector, linker, and polyA sequences and by masking ambiguous bases, using algorithms and programs based on BLAST,

dynamic programing, and dinucleotide nearest neighbor analysis. The sequences were then queried against a selection of public databases, such as the GenBank primate, rodent, mammalian, vertebrate, and eukaryote databases, and BLOCKS to acquire annotation using programs based on BLAST, FASTA, and BLIMPS. The sequences were assembled into full length polynucleotide sequences using programs based on Phred, Phrap, and Consed, and were screened for open reading frames using programs based on GeneMark, BLAST, and FASTA. The full length polynucleotide sequences were translated to derive the corresponding full length amino acid sequences, and these full length sequences were subsequently analyzed by querying against databases such as the GenBank databases (described above), SwissProt, BLOCKS, PRINTS, Prosite, and Hidden Markov Model (HMM)-based protein family databases such as PFAM. HMM is a probabilistic approach which analyzes consensus primary structures of gene families. (See, e.g., Eddy, S.R. (1996) Curr. Opin. Str. Biol. 6:361-365.)

The programs described above for the assembly and analysis of full length polynucleotide and amino acid sequences were also used to identify polynucleotide sequence fragments from SEQ ID NO:32-62. Fragments from about 20 to about 4000 nucleotides which are useful in hybridization and amplification technologies were described in The Invention section above.

### IV. Northern Analysis

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Northern analysis is a laboratory technique used to detect the presence of a transcript of a gene and involves the hybridization of a labeled nucleotide sequence to a membrane on which RNAs from a particular cell type or tissue have been bound. (See, e.g., Sambrook, supra, ch. 7; Ausubel, 20 1995, supra, ch. 4 and 16.)

Analogous computer techniques applying BLAST were used to search for identical or related molecules in nucleotide databases such as GenBank or LIFESEQ database (Incyte Pharmaceuticals). This analysis is much faster than multiple membrane-based hybridizations. In addition, the sensitivity of the computer search can be modified to determine whether any particular match is categorized as exact or similar. The basis of the search is the product score, which is defined as:

### % sequence identity x % maximum BLAST score

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The product score takes into account both the degree of similarity between two sequences and the length of the sequence match. For example, with a product score of 40, the match will be exact within a 1% to 2% error, and, with a product score of 70, the match will be exact. Similar molecules are usually identified by selecting those which show product scores between 15 and 40, although lower scores may identify related molecules.

The results of northern analyses are reported as a percentage distribution of libraries in which the transcript encoding PHSP occurred. Analysis involved the categorization of cDNA libraries by organ/tissue and disease. The organ/tissue categories included cardiovascular, dermatologic,

developmental, endocrine, gastrointestinal, hematopoietic/immune, musculoskeletal, nervous, reproductive, and urologic. The disease/condition categories included cancer, inflammation/trauma, cell proliferation, neurological, and pooled. For each category, the number of libraries expressing the sequence of interest was counted and divided by the total number of libraries across all categories. Percentage values of tissue-specific and disease- or condition-specific expression are reported in Table 3.

### V. **Extension of PHSP Encoding Polynucleotides**

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The full length nucleic acid sequences of SEQ ID NO:32-62 were produced by extension of an appropriate fragment of the full length molecule using oligonucleotide primers designed from this 10 fragment. One primer was synthesized to initiate 5' extension of the known fragment, and the other primer, to initiate 3' extension of the known fragment. The initial primers were designed using OLIGO 4.06 software (National Biosciences), or another appropriate program, to be about 22 to 30 nucleotides in length, to have a GC content of about 50% or more, and to anneal to the target sequence at temperatures of about 68°C to about 72°C. Any stretch of nucleotides which would result in hairpin structures and primer-primer dimerizations was avoided.

Selected human cDNA libraries were used to extend the sequence. If more than one extension was necessary or desired, additional or nested sets of primers were designed.

High fidelity amplification was obtained by PCR using methods well known in the art. PCR was performed in 96-well plates using the PTC-200 thermal cycler (MJ Research, Inc.). The reaction 20 mix contained DNA template, 200 nmol of each primer, reaction buffer containing Mg<sup>2+</sup>, (NH<sub>4</sub>)<sub>2</sub>SO<sub>4</sub>, and β-mercaptoethanol, Taq DNA polymerase (Amersham Pharmacia Biotech), ELONGASE enzyme (Life Technologies), and Pfu DNA polymerase (Stratagene), with the following parameters for primer pair PCI A and PCI B: Step 1: 94°C, 3 min; Step 2: 94°C, 15 sec; Step 3: 60°C, 1 min; Step 4: 68°C, 2 min; Step 5: Steps 2, 3, and 4 repeated 20 times; Step 6: 68°C, 5 min; Step 7: storage at 4°C. In the alternative, the parameters for primer pair T7 and SK+ were as follows: Step 1: 94°C, 3 min; Step 2: 94°C, 15 sec; Step 3: 57°C, 1 min; Step 4: 68°C, 2 min; Step 5: Steps 2, 3, and 4 repeated 20 times; Step 6: 68°C, 5 min; Step 7: storage at 4°C.

The concentration of DNA in each well was determined by dispensing 100 µl PICOGREEN quantitation reagent (0.25% (v/v) PICOGREEN; Molecular Probes, Eugene OR) dissolved in 1X TE 30 and 0.5 μl of undiluted PCR product into each well of an opaque fluorimeter plate (Corning Costar, Acton MA), allowing the DNA to bind to the reagent. The plate was scanned in a Fluoroskan II (Labsystems Oy, Helsinki, Finland) to measure the fluorescence of the sample and to quantify the concentration of DNA. A 5  $\mu$ l to 10  $\mu$ l aliquot of the reaction mixture was analyzed by electrophoresis on a 1 % agarose mini-gel to determine which reactions were successful in extending the sequence.

The extended nucleotides were desalted and concentrated, transferred to 384-well plates, digested with CviJI cholera virus endonuclease (Molecular Biology Research, Madison WI), and sonicated or sheared prior to religation into pUC 18 vector (Amersham Pharmacia Biotech). For shotgun sequencing, the digested nucleotides were separated on low concentration (0.6 to 0.8%) agarose gels, fragments were excised, and agar digested with Agar ACE (Promega). Extended clones were religated using T4 ligase (New England Biolabs, Beverly MA) into pUC 18 vector (Amersham Pharmacia Biotech), treated with Pfu DNA polymerase (Stratagene) to fill-in restriction site overhangs, and transfected into competent <u>E. coli</u> cells. Transformed cells were selected on antibiotic-containing media, individual colonies were picked and cultured overnight at 37°C in 384-well plates in LB/2x carb liquid media.

The cells were lysed, and DNA was amplified by PCR using Taq DNA polymerase (Amersham Pharmacia Biotech) and Pfu DNA polymerase (Stratagene) with the following parameters: Step 1: 94°C, 3 min; Step 2: 94°C, 15 sec; Step 3: 60°C, 1 min; Step 4: 72°C, 2 min; Step 5: steps 2, 3, and 4 repeated 29 times; Step 6: 72°C, 5 min; Step 7: storage at 4°C. DNA was quantified by PICOGREEN reagent (Molecular Probes) as described above. Samples with low DNA recoveries were reamplified using the same conditions as described above. Samples were diluted with 20% dimethysulphoxide (1:2, v/v), and sequenced using DYENAMIC energy transfer sequencing primers and the DYENAMIC DIRECT kit (Amersham Pharmacia Biotech) or the ABI PRISM BIGDYE Terminator cycle sequencing ready reaction kit (Perkin-Elmer).

In like manner, the nucleotide sequences of SEQ ID NO:32-62 are used to obtain 5' regulatory sequences using the procedure above, oligonucleotides designed for such extension, and an appropriate genomic library.

### VI. Labeling and Use of Individual Hybridization Probes

Hybridization probes derived from SEQ ID NO:32-62 are employed to screen cDNAs, genomic DNAs, or mRNAs. Although the labeling of oligonucleotides, consisting of about 20 base pairs, is specifically described, essentially the same procedure is used with larger nucleotide fragments. Oligonucleotides are designed using state-of-the-art software such as OLIGO 4.06 software (National Biosciences) and labeled by combining 50 pmol of each oligomer, 250 μCi of [γ-32P] adenosine triphosphate (Amersham Pharmacia Biotech), and T4 polynucleotide kinase (DuPont NEN, Boston MA). The labeled oligonucleotides are substantially purified using a SEPHADEX G-25 superfine size exclusion dextran bead column (Amersham Pharmacia Biotech). An aliquot containing 10<sup>7</sup> counts per minute of the labeled probe is used in a typical membrane-based hybridization analysis of human genomic DNA digested with one of the following endonucleases: Ase I, Bgl II, Eco RI, Pst I, Xba1, or Pvu II (DuPont NEN).

The DNA from each digest is fractionated on a 0.7% agarose gel and transferred to nylon

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membranes (Nytran Plus, Schleicher & Schuell, Durham NH). Hybridization is carried out for 16 hours at 40°C. To remove nonspecific signals, blots are sequentially washed at room temperature under increasingly stringent conditions up to 0.1 x saline sodium citrate and 0.5% sodium dodecyl sulfate. Hybridization patterns are compared.

### 5 VII. Microarrays

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A chemical coupling procedure and an ink jet device can be used to synthesize array elements on the surface of a substrate. (See, e.g., Baldeschweiler, supra.) An array analogous to a dot or slot blot may also be used to arrange and link elements to the surface of a substrate using thermal, UV, chemical, or mechanical bonding procedures. A typical array may be produced by hand 10 or using available methods and machines and contain any appropriate number of elements. After hybridization, nonhybridized probes are removed and a scanner used to determine the levels and patterns of fluorescence. The degree of complementarity and the relative abundance of each probe which hybridizes to an element on the microarray may be assessed through analysis of the scanned images.

Full-length cDNAs, Expressed Sequence Tags (ESTs), or fragments thereof may comprise the elements of the microarray. Fragments suitable for hybridization can be selected using software well known in the art such as LASERGENE software (DNASTAR). Full-length cDNAs, ESTs, or fragments thereof corresponding to one of the nucleotide sequences of the present invention, or selected at random from a cDNA library relevant to the present invention, are arranged on an 20 appropriate substrate, e.g., a glass slide. The cDNA is fixed to the slide using, e.g., UV cross-linking followed by thermal and chemical treatments and subsequent drying. (See, e.g., Schena, M. et al. (1995) Science 270:467-470; Shalon, D. et al. (1996) Genome Res. 6:639-645.) Fluorescent probes are prepared and used for hybridization to the elements on the substrate. The substrate is analyzed by procedures described above.

### 25 VIII. Complementary Polynucleotides

Sequences complementary to the PHSP-encoding sequences, or any parts thereof, are used to detect, decrease, or inhibit expression of naturally occurring PHSP. Although use of oligonucleotides comprising from about 15 to 30 base pairs is described, essentially the same procedure is used with smaller or with larger sequence fragments. Appropriate oligonucleotides are designed using OLIGO 4.06 software (National Biosciences) and the coding sequence of PHSP. To inhibit transcription, a complementary oligonucleotide is designed from the most unique 5' sequence and used to prevent promoter binding to the coding sequence. To inhibit translation, a complementary oligonucleotide is designed to prevent ribosomal binding to the PHSP-encoding transcript.

### IX. **Expression of PHSP**

Expression and purification of PHSP is achieved using bacterial or virus-based expression 35

systems. For expression of PHSP in bacteria, cDNA is subcloned into an appropriate vector containing an antibiotic resistance gene and an inducible promoter that directs high levels of cDNA transcription. Examples of such promoters include, but are not limited to, the trp-lac (tac) hybrid promoter and the T5 or T7 bacteriophage promoter in conjunction with the lac operator regulatory element. Recombinant vectors are transformed into suitable bacterial hosts, e.g., BL21(DE3). Antibiotic resistant bacteria express PHSP upon induction with isopropyl beta-Dthiogalactopyranoside (IPTG). Expression of PHSP in eukaryotic cells is achieved by infecting insect or mammalian cell lines with recombinant Autographica californica nuclear polyhedrosis virus (AcMNPV), commonly known as baculovirus. The nonessential polyhedrin gene of baculovirus is replaced with cDNA encoding PHSP by either homologous recombination or bacterial-mediated transposition involving transfer plasmid intermediates. Viral infectivity is maintained and the strong polyhedrin promoter drives high levels of cDNA transcription. Recombinant baculovirus is used to infect Spodoptera frugiperda (Sf9) insect cells in most cases, or human hepatocytes, in some cases. Infection of the latter requires additional genetic modifications to baculovirus. (See Engelhard, E. K. 15 et al. (1994) Proc. Natl. Acad. Sci. USA 91:3224-3227; Sandig, V. et al. (1996) Hum. Gene Ther. 7:1937-1945.)

In most expression systems, PHSP is synthesized as a fusion protein with, e.g., glutathione S-transferase (GST) or a peptide epitope tag, such as FLAG or 6-His, permitting rapid, single-step, affinity-based purification of recombinant fusion protein from crude cell lysates. GST, a 26-20 kilodalton enzyme from Schistosoma japonicum, enables the purification of fusion proteins on immobilized glutathione under conditions that maintain protein activity and antigenicity (Amersham Pharmacia Biotech). Following purification, the GST moiety can be proteolytically cleaved from PHSP at specifically engineered sites. FLAG, an 8-amino acid peptide, enables immunoaffinity purification using commercially available monoclonal and polyclonal anti-FLAG antibodies (Eastman Kodak). 6-His, a stretch of six consecutive histidine residues, enables purification on metal-chelate resins (QIAGEN). Methods for protein expression and purification are discussed in Ausubel (1995, supra, ch 10 and 16). Purified PHSP obtained by these methods can be used directly in the following activity assay.

### X. Demonstration of PHSP Activity

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PHSP protein kinase is measured by the phosphorylation of a substrate in the presence of gamma-labeled <sup>32</sup>P-ATP. PHSP is incubated with an appropriate substrate and <sup>32</sup>P-ATP in a buffered solution. <sup>32</sup>P-labeled product is separated from free <sup>32</sup>P-ATP by gel electrophoresis or chromatographic procedures, and the incorporated <sup>32</sup>P is quantified by phosphorimage analysis or using a scintillation counter. The amount of <sup>32</sup>P detected is proportional to the activity of PHSP in this assay. The specific amino acid residue phosphorylated by PHSP may be determined by

phosphoamino acid analysis of the labeled, hydrolyzed protein.

PHSP phosphatase activity is measured by the removal of phosphate from a [32P]-labelled substrate. PHSP is incubated with an appropriate [32P]-labelled substrate in a buffered solution. Reaction products are separated by gel electrophoresis or chromatographic procedures, and the level of 32P associated with the substrate molecule is quantified by phospho-image analysis or scintillation counting. The difference in 32P associated with untreated substrate versus PHSP-treated substrate is a measure of phosphatase activity and is proportional to PHSP activity.

### XI. Functional Assays

PHSP function is assessed by expressing the sequences encoding PHSP at physiologically elevated levels in mammalian cell culture systems. cDNA is subcloned into a mammalian expression vector containing a strong promoter that drives high levels of cDNA expression. Vectors of choice include pCMV SPORT (Life Technologies) and pCR3.1 (Invitrogen, Carlsbad CA), both of which contain the cytomegalovirus promoter.  $5-10~\mu g$  of recombinant vector are transiently transfected into a human cell line, preferably of endothelial or hematopoietic origin, using either liposome 15 formulations or electroporation. 1-2  $\mu$ g of an additional plasmid containing sequences encoding a marker protein are co-transfected. Expression of a marker protein provides a means to distinguish transfected cells from nontransfected cells and is a reliable predictor of cDNA expression from the recombinant vector. Marker proteins of choice include, e.g., Green Fluorescent Protein (GFP; Clontech), CD64, or a CD64-GFP fusion protein. Flow cytometry (FCM), an automated, laser optics-20 based technique, is used to identify transfected cells expressing GFP or CD64-GFP and to evaluate properties, for example, their apoptotic state. FCM detects and quantifies the uptake of fluorescent molecules that diagnose events preceding or coincident with cell death. These events include changes in nuclear DNA content as measured by staining of DNA with propidium iodide; changes in cell size and granularity as measured by forward light scatter and 90 degree side light scatter; down-regulation of DNA synthesis as measured by decrease in bromodeoxyuridine uptake; alterations in expression of cell surface and intracellular proteins as measured by reactivity with specific antibodies; and alterations in plasma membrane composition as measured by the binding of fluorescein-conjugated Annexin V protein to the cell surface. Methods in flow cytometry are discussed in Ormerod, M. G. (1994) Flow Cytometry, Oxford, New York NY.

The influence of PHSP on gene expression can be assessed using highly purified populations of cells transfected with sequences encoding PHSP and either CD64 or CD64-GFP. CD64 and CD64-GFP are expressed on the surface of transfected cells and bind to conserved regions of human immunoglobulin G (IgG). Transfected cells are efficiently separated from nontransfected cells using magnetic beads coated with either human IgG or antibody against CD64 (DYNAL, Lake Success NY). mRNA can be purified from the cells using methods well known by those of skill in the art.

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Expression of mRNA encoding PHSP and other genes of interest can be analyzed by northern analysis or microarray techniques.

### XII. Production of PHSP Specific Antibodies

PHSP substantially purified using polyacrylamide gel electrophoresis (PAGE; see, e.g., Harrington, M.G. (1990) Methods Enzymol. 182:488-495), or other purification techniques, is used to immunize rabbits and to produce antibodies using standard protocols.

Alternatively, the PHSP amino acid sequence is analyzed using LASERGENE software (DNASTAR) to determine regions of high immunogenicity, and a corresponding oligopeptide is synthesized and used to raise antibodies by means known to those of skill in the art. Methods for selection of appropriate epitopes, such as those near the C-terminus or in hydrophilic regions are well described in the art. (See, e.g., Ausubel, 1995, supra, ch. 11.)

Typically, oligopeptides 15 residues in length are synthesized using an ABI 431A peptide synthesizer (Perkin-Elmer) using fmoc-chemistry and coupled to KLH (Sigma-Aldrich, St. Louis MO) by reaction with N-maleimidobenzoyl-N-hydroxysuccinimide ester (MBS) to increase immunogenicity. (See, e.g., Ausubel, 1995, <a href="mailto:supra">supra</a>.) Rabbits are immunized with the oligopeptide-KLH complex in complete Freund's adjuvant. Resulting antisera are tested for antipeptide activity by, for example, binding the peptide to plastic, blocking with 1% BSA, reacting with rabbit antisera, washing, and reacting with radio-iodinated goat anti-rabbit IgG.

### XIII. Purification of Naturally Occurring PHSP Using Specific Antibodies

Naturally occurring or recombinant PHSP is substantially purified by immunoaffinity chromatography using antibodies specific for PHSP. An immunoaffinity column is constructed by covalently coupling anti-PHSP antibody to an activated chromatographic resin, such as CNBr-activated SEPHAROSE (Amersham Pharmacia Biotech). After the coupling, the resin is blocked and washed according to the manufacturer's instructions.

Media containing PHSP are passed over the immunoaffinity column, and the column is washed under conditions that allow the preferential absorbance of PHSP (e.g., high ionic strength buffers in the presence of detergent). The column is eluted under conditions that disrupt antibody/PHSP binding (e.g., a buffer of pH 2 to pH 3, or a high concentration of a chaotrope, such as urea or thiocyanate ion), and PHSP is collected.

### 30 XIV. Identification of Molecules Which Interact with PHSP

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PHSP, or biologically active fragments thereof, are labeled with <sup>125</sup>I Bolton-Hunter reagent. (See, e.g., Bolton et al. (1973) Biochem. J. 133:529.) Candidate molecules previously arrayed in the wells of a multi-well plate are incubated with the labeled PHSP, washed, and any wells with labeled PHSP complex are assayed. Data obtained using different concentrations of PHSP are used to calculate values for the number, affinity, and association of PHSP with the candidate molecules.

Various modifications and variations of the described methods and systems of the invention will be apparent to those skilled in the art without departing from the scope and spirit of the invention. Although the invention has been described in connection with specific preferred embodiments, it should be understood that the invention as claimed should not be unduly limited to such specific embodiments. Indeed, various modifications of the described modes for carrying out the invention which are obvious to those skilled in molecular biology or related fields are intended to be within the scope of the following claims.

### TABLE

Protein SEQ ID NO:	Nucleotide SEQ ID NO:	Clone ID	Library	Fragments
1	32	132240	BMARNOT02	132240H1 and 132240R1 (BMARNOT02), 3254142H1 (OVARTUN01), 1453821X14F1 and 1453821F6 (PENITUT01)
2	33	2180116	SININOT01	2180116H1 and 2180116T6 (SININOT01), 3046645H1 (HEAANOT01), 1918183H1 (PROSNOT06), and 1482405F1 (CORPNOT02)
3	34	2197671	SPLNFET02	2197671H1 (SPLNFET02), 666366X22R1 (SCORNOT01), 693783X14 (SYNORAT03), 824265X33F1 (PROSNOT06), 039482R1 and 039482F1 (HUVENOB01), 1453984T6 (PENITUT01), 1663987H1 (BRSTNOT09), and 125901R1 (LUNGNOT01)
4	35	2594943	OVARTUT02	2594943H1 (OVARTUT02), 3617557H1 (EPIPNOT01), 2269005R6 (UTRSNOT02), 1307764F6 (COLNFET02), 1377794F6 (LUNGNOT10), and 1286608H1 (BRAINOT11)
5	36	1513871	PANCTUT01	754239R6 (BRAITUT02), 1513871H1 (PANCTUT01), 2414420F6 (HNT3AZT01), 3291775F6 (BONRFET01), 3821451F6 (BONSTUT01)
9	37	156108	тнр1Рьв02	156108F1 and 156108H1 (THP1PLB02), 336346R6 (EOSIHET02), 1319528F1 (BLADNOT04), 2375549F6 (ISLTNOT01), SBFA04563F1, SBFA04977F1
7	38	2883243	UTRSTUT05	1342082F6 (COLNTUTO3), 1933387T6 (COLNNOT16), 2766460F6 (BRSTNOT12), 2883243H1 (UTRSTUT05), 3524262H1 (ESOGTUN01), 3766487F6 (BRSTNOT24)

Protein SEQ ID NO:	Nucleotide SEQ ID NO:	Clone ID	Library	Fragments
ω	39	3173355	UTRSTUT04	1300803F6 and 1300803T6 (BRSTNOT07), 2477542F6 (SMCANOT01), 2477542T6 (SMCANOT01), 2875968H1 (THYRNOT10), 3173355F6 and 3173355H1 (UTRSTUT04), 3290825H1 (BONRFET01), 5192561H1 (OVARDIT06)
6	40	5116906	SMCBUNT01	267517F1 (HNT2NOT01), 263823R1 (HNT2AGT01), 5116906H1 (SMCBUNT01)
10	41	940589	ADREMOT03	029801R6 (SPLNFET01), 940589H1 (ADRENOT03), 1737403T6 (COLNNOT22), 1805477F6 and 1805477T6 (SINTNOT13), 2447613H1 (THP1NOT03), 3408563H1 (PROSTUS08), 3519506H1 (LUNGNON03), 3637343T6 (LUNGNOT30)
11	42	304421	TESTNOT04	304421H1, 304421X318B2, and 304421X323B2 (TESTNOT04), 2639579F6 (BONTNOT01), 2951859H1 (KIDNFET01)
12	43	1213802	BRSTTUT01	894574R1 (BRSTNOTO5), 1213802H1 (BRSTTUTO1), 1233414F1 and 1234238H1 (LUNGFETO3), 1255782F2 and 1255782T1 (MENITUTO3), 1455429F1 (COLNFETO2), 1576102T1 (LNODNOTO3), 2189267F6 (PROSNOT26), 2748179F6 (LUNGTUT11), 2831667H1 (TLYMNOTO3), 3031229H1 (TLYMNOTO5), 3054893H1 (LNODNOTO8), 3797030F6 (SPLNNOT12), 3880154H1 (SPLNNOT11), 4852525H1 (TESTNOT10), 5514137H1 (BRADDIR01), 5518378H1
13	44	1378134	LUNGNOT10	1378134H1 and 1378134X11 (LUNGNOT10), 2205185F6 (SPLNFET02), 4959694H1 (TLYMNOT05), SAMA00107F1, SAMA00160F1, SAMA00020F1

Protein SEQ ID NO:	Nucleotide SEQ ID NO:	Clone ID	Library	Fragments
14	45	1490070	UCMCL5T01	432218H1 (BRAVUNTO2), 1490070H1 (UCMCL5T01), 1535394F1 (SPLNNOT04), 1616509F6 and 1616509T6 (BRAITUT12), 2490845H1 (EOSITXT01), 2723789F6 (LUNGTUT10), SAOA00263F1
15	46	1997814	BRSTTUT03	855350R1 (NGANNOT01), 875417R1 (LUNGAST01), 895096R1 (BRSTNOT05), 1271348F1 (TESTTUT02), 1331289F6 (PANCNOT07), 1359243F1 (LUNGNOT12), 1540824T1 (SINTTUT01), 1839828H1 (EOSITXT01), 1997814H1 (BRSTTUT03), 2170638F6 (ENDCNOT03), 3751363F6 (UTRSNOT18)
16	47	2299715	BRSTNOT05	637354R6 and 637354T6 (NEUTGMT01), 1852144F6 (LUNGFET03), 2172576F6 (ENDCNOT03), 2232449F6 (PROSNOT16), 2299715H1 (BRSTNOT05), 2509737X325D2 (CONUTUT01), 2606210F6 (LUNGTUT07), 2692024F6 (LUNGNOT23), 2805893F6 (BLADTUT08), 2986160H1 (CARGDIT01), 3085382H1 (HEAONOT03), 3136101F6 and 3136587H1 (SMCCNOT01), 4249977H1 (BRADDIR01)
17	48	209854	SPLNNOT02	209854H1 and 209854T6 (SPLNNOT02), 3152165R6 and 3152165T6 (ADRENON04)
18	49	1384286	BRAITUT08	676123R6 and 676123T6 (CRBLNOT01), 989218X11 and 989218X12 (LVENNOT03), 1384286H1 (BRAITUT08), 3099868H1 (PROSBPT03), 4693167H1 (BRAENOT02)
19	50	1512656	PANCTUT01	322847X5 (EOSIHET02), 1253795T6 (LUNGFET03), 1512656H1 (PANCTUT01), 1561686X303D1 (SPLNNOT04), 2212305H1 (SINTFET03), 2697679H1 (UTRSNOT12), 3205172H1 (PENCNOT03), 5313318H1 (KIDETXS02)

Protein SEQ ID NO:	Nucleotide SEQ ID NO:	Clone ID	Library	Fragments
20	51	2098635	BRAITUT02	1268848T1, 1268848X301F1, and 2157157H1 (BRAINOT09), 2098635H1 and 2098635R6 (BRAITUT02), 2198819F6, 2198819X301D4, 2198819X309B2, and 2198819X309D4 (SPLNFET02), 2784975H2 (BRSTNOT13), 3320340H1 (PROSBPT03)
21	52	2446646	THP1NOT03	000297R6 and 000297X61 (U937NOT01), 2446646H1 (THP1NOT03), 2557274F6 (THYMNOT03)
22	53	2764911	BRSTNOT12	678618T6 and 678618X14 (UTRSNOT02), 2304126R6 (BRSTNOT05), 2764911H1 (BRSTNOT12), 2834475F6 (TLYMNOT03), 2915803F6 (THYMFET03), 3035012F6 (TLYMNOT05), SAFC00027F1, SAFC00254F1, SAFC02376F1, SAFC01609F1
23	54	3013946	MUSCNOT07	673753H1 (CRBLNOT01), 989218X11 and 989218X14 (LVENNOT03), 2821720F6 (ADRETUT06), 3013946F6, 3013946H1, and 3013946T6 (MUSCNOT07), 4693167H1 (BRAENOT02)
24	55	196190	HUVESTB01	067967x92, 067966R1, and 067967H1 (HUVESTB01), SAIA02074F1, SAIA03254F1, SAIA03603F1, and SAIA02259F1
25	56	346275	THYMNOT02	346275H1 (THYMNOT02), 609792X12 (COLNNOT01), SAGA03543F1, SAGA02528F1, and SAGA00285F1
26	57	283746	CARDNOT01	283746H1 and 283746X10 (CARDNOT01), 4903108H1 (TLYMNOT08), 557918X15 (MPHGLPT02), and 2379045F6 (ISLTNOT01)
27	58	2696537	UTRSNOT12	2696537H1 (UTRSNOT12), 3173337F6 (UTRSTUT04), 082658X100 (HUVESTB01), and 603219T6 (BRSTTUT01)

Protein SEQ ID NO:	Nucleotide SEQ ID NO:	Clone ID Library	Library	Fragments
28	59	551178	BEPINOT01	551178H1 (BEPINOT01), 861522R1 (BRAITUT03), 965838R1 (BRSTNOT05), 1574007F1 (LNODNOT03), 1830083T6 and 1831194T6 (THP1AZT01), 3098496H1 (CERVNOT03), 3293481H1 (TLYJINT01)
29	9	619292	PGANNOT01	613165F1 (COLNTUT02), 619292H1 and 619292X13 (PGANNOT01)
30	61	2054049	BEPINOT01	1736355F6 (COLNNOT22), 2054049H1 (BEPINOT01), 2379092T6 (ISLTNOT01), 3127284T3 (LUNGTUT12), 3136377F6 (SMCCNOT01), SBMA00545F1, SBMA00827F1, SBMA02930F1, SBMA02853F1
31	62	2843910	DRGLNOT01	036294X71 (HUVENOB01), 066017X102, 068399R1, and 068399X3 (HUVESTB01), 1527276H1 (UCMCL5T01), 1846570T6 (COLNNOT09), 2843910H1 (DRGLNOT01)

### ABLE 2

Polypeptide SEQ ID NO:	Amino Acid Residues	Potential Potential Phosphorylation Sites	Potential Glycosylation Sites	Signature Sequence	Homologous sequences	Analytical Methods
1	300	S3 S15 S19 S20 S24 T98 S125 S231 T238 S257 S282 S12 S41 S70 T120 T143 S146 T242	N85 N88 N96	Protein kinase motifs: G161-F256 catalytic tk domain IX: V180-E202	Protein Kinase	BLAST PFAM PRINTS
2	147	S85 T38 S90		Calcium-binding repeat motifs: G28-L115	PKC- potentiated inhibitory protein of PP1 (CPI17)	BLAST PRINTS BLOCKS
m	431	T178 S282 T25 S34 S75 S106 S194 S198 T208 T264 S299 S303 S304 S308 T328 S345 S388 T46 S137 S260	N44 N242	PTK signatures: A18-Y283 ATP-binding site: I30-K53, E127-G164 Y196-H219 PK catalytic subdomains: M99-E112, Y134-L152 G181-I191, Y243-	Ste20-like protein kinase	BLOCKS PRINTS PROFILESCAN BLAST
4	218	S108 S68 S90 T133 T170 S172 T34 T123 T207		Phosphofructokinase domains: I47, V177-Q195 L148-Y164		PRINTS

Polypeptide SEQ ID NO:	Amino Acid Residues	Potential Phosphorylation Sites	Potential Glycosylation Sites	Signature Sequence	Homologous sequences	Analytical Methods
v	474	S14 S89 S98 S132 S472 T22 S26 S62 S66 T204 T320 T345 T359 S427 S443 S94 S128 T211 T336 S443 Y155		Protein kinase family signature: Y144-F425	serine /threonine protein kinase	MOTIFS PFAM BLOCKS PRINTS ProfileScan BLAST
9	540	S102 S183 S267 T296 T301 S442 S34 S58 S180 S207 S224 T360 S374 S401 S428 S478 T484 Y23	N100 N391 N457 N537	Protein kinase family signature: L18-L287	serine /threonine protein kinase	MOTIFS PFAM BLOCKS PRINTS PROFILESCAN BLAST
7	454	S57 S69 S130 T203 T212 S338 S420 S91 T101 T220 S271 S295 T315 S359 S381 Y197	N55 N140 N218 N403 N437 N441	SH2 domain: W63-Y138, W354-Y428 PI 3 kinase P85 regulator: K153-G176, A216- N257, R287-N332	phosphatidyl- inositol 3- kinase	PFAM BLOCKS PRINTS BLAST
∞	502	S246 T498 T21 S65 S76 T193 T203 S275 S312 S355 T484 S106 T222 S323 T498 Y347	N302 N414	Signal petide: M1-T21 SH2 domain: V70-E80 ER targeting signal: K499-L502	tyrosine kinase	SigPept BLOCKS MOTIFS BLAST

Polypeptide SEQ ID NO:	Amino Acid Residues	Potential Potential Phosphorylation Glycosylation Sites	Potential Glycosylation Sites	Signature Sequence	Homologous sequences	Analytical Methods
o.	281	T66 T140 T141 T182 S210	N117 N139	Signal peptide: M1-176	calcium /calmodulin- dependent protein kinase	PFAM BLAST
10	510	T297 S323 S358 S51 T312 S323 T325 S329 T377 T390 T483 S24 S152 T201 S210 S247 T292 T406 T407	N185 N349 N381 N405	Protein kinase family signature: R52-V261	Serine /threonine protein kinase	PFAM BLOCKS PRINTS MOTIFS BLAST
11	248	S5 S20 S36 T210 N208 T245	N208	Tyrosine specific phosphatase active site: F166-A220 Dual specificity phosphatase: H95-R240	Tyrosine phosphatase or Dual specificity phosphatase	BLAST, MOTIFS BLOCKS, PRINTS PROFILESCAN PFAM

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Polypeptide SEQ ID NO:	Amino Acid Residues	Potential Phosphorylation Sites	Potential Glycosylation Sites	Signature Sequence	Homologous sequences	Analytical Methods
12	810	\$62 \$290 T429 \$758 T17 T104 \$108 T216 \$279 T316 \$330 T360 \$386 T405 \$425 \$465 T473 \$497 T547 T561 T715 \$733 \$738 \$768 \$196 \$222 \$229 \$267 T281 T321 T347 \$370 T400 T512 \$534 T609 \$617 \$663 \$751	N33		Protein kinase	BLAST, MOTIFS
13	549	S6 T502 T21 T116 S125 S320 T417 S46 S87 T240 S390 S397 S405 S430 S497	N238	ATP/GTP-binding site (p-loop): G58-T65 Protein kinase signature: I176-K199 I292-L304 Y347-L370 F456-L483	Dual specificity tyrosine /serine protein kinase	BLAST, MOTIFS BLOCKS, PRINTS PFAM
14	416	S312 T20 T97 S104 S183 T185 T211 T274 S381 S411 S72 S79 S140 S318 Y53		SH3 domain: A366-D384 N402-E414	PEST phosphatase interacting protein	BLAST, MOTIFS BLOCKS, PRINTS PFAM

Analytical Methods	BLAST, MOTIFS	BLAST, MOTIFS PROFILESCAN BLOCKS, PRINTS PFAM	BLAST
Homologous sequences	SH3 binding protein	NIK kinase	Interferon- induced PK regulator (P52rIPK)
Signature Sequence		Protein kinase signature: V31-K54 V149-L161 W129-V182 Tyrosine kinase catalytic site: G190-I200 S214-M236 NIK1-like kinase domain: Y836-R1115	
Potential Glycosylation Sites	N23 N176 N362	N33 N570 N718	N19 N100 N114
Potential Phosphorylation Sites	T34 S233 S234 S25 S107 T144 T198 T250 S251 S258 S282 S300 S324 S345 T390 T51 T133 S365 S383 Y71	S57 T187 S259 S554 S815 S9 S17 T59 S112 T124 T222 S264 T319 S324 S326 S550 T572 S625 S681 S682 T688 T689 S706 S720 T931 S958 S978 S999 S255 T309 T351 T543 S550 S624 S632 S726 T351 T543 S550 S624 S632 S726 T351 T543 S550	T163 S60 T78 T68 S88 S147
Amino Acid Residues	425	1135	228
Polypeptide SEQ ID NO:	15	16	17

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Polypeptide SEQ ID NO:	Amino Acid Residues	Potential Potential Phosphorylation Glycosylation Sites	Potential Glycosylation Sites	Signature Sequence	Homologous sequences	Analytical Methods
18	503	S51 T262 T36 S79 T94 S109 T361 T362 T403 S472 T47 S334 S343 Y17	N313 N333 N360	Protein kinase signature: I20-K43 V132-L144 V195-E217 Protein kinase domain: Y14-V272	calcium /calmodulin- dependent protein kinase II, beta 3 isoform	BLAST, BLOCKS, PRINTS, MOTIFS, PFAM, PROFILESCAN
19	433	S12 S77 S124 S131 S255 S290 T327 S365 S402 T70 Y88			Choline kinase isolog 384D8_3	BLAST, MOTIFS
20	527	S417 S154 S199 T367 S453 T120 S178 S413 T447 S473	N470	Protein kinase signature: 1144-K167 1260-V172 ATP-binding site: Q247-G284 Y318-F341 Protein kinase domain: 1138-L427	MAP-related protein kinase	BLAST, BLOCKS MOTIFS, PFAM, PROFILESCAN

Polypeptide	Amino	Potential phosphorylation	Potential	Signature Sequence	Homologous	Analytical Methods
SEQ ID NO:	Residues	Fnosphory racion Sites	Sites			
21	322	S19 S122 T198 T200 T236 S251	N196 N249	Protein kinase signature:	Protein tyrosine	
		T260 S264 T301			kinase	MOTIFS, PFAM,
		S14 S52 T181 T225		ATP-binding site: M150-V187		PROFILESCAN
		1		I224-H247		
				Protein kinase domain:		
				0101-300		i
22	802	T87 S7	N36 N655	Protein kinase	Ribosomal S6	BLAST, BLOCKS,
		r98 S1		signature:	protein kinase	
		\$230		L55-K81, L432-K455		MOTIFS, PFAM,
		T353 T465 T470		ATP-binding site:		PROFILESCAN
				E160-G197, H232-F255		
				PTK catalytic domain:		
		T100 T207 S268		H534-F552, C603-H625		
		S368 S458		Protein kinase domains:		
				F49-F318, L427-L687		
		-		Protein kinase C		
				domain:		
				Q319-I382		
23	641	S51 T262 S398	N313 N332	Protein kinase	Ca2+	BLAST, BLOCKS,
		S436 S479 T36	N374	signature:	/calmodulin	PRINTS,
		S79 T94 S109		I20-K43	dependent	MOTIFS, PFAM,
		T375 T376 T541		V132-L144	protein kinase	PROFILESCAN
		S610 T47 S315		ATP-binding site:		
		S333 S342 S393		Q119-A156		
		S422 S431 S465		Y191-F214		
		S474 S508 Y17		Protein kinase domain:		
				Y14-V272		

Polypeptide SEQ ID NO:	Amino Acid Residues	Potential Potential Phosphorylation Sites	Potential Glycosylation Sites	Signature Sequence	Homologous sequences	Analytical Methods
24	288	S106 T155 S359 T388 T456 T531 T4, S58 S108 T126 S132 T279 S350 S436 S469 S508 S537 Y32	N63 N130 N574	Protein kinase catalytic domain: Y209-S445, F495-I522 ATP-binding site: I215-K238 STK core catalytic motif: I331-L343	Protein kinase Dyrk2	MOTIFS PFAM BLOCKS PRINTS BLAST
25	389	S31 T301 S56 S96 S134 T149 S186 S201 S283 S358 S375 Y148 Y165	N257 N343 N364	Protein kinase catalytic domain: E73-1311 STK core catalytic motif: 1172-Y184 PTK core domain: D152-D208	CaM-like protein kinase	BLAST PFAM MOTIFS BLOCKS PRINTS PROFILESCAN
26	343	S68 S81 S137 S184 T219 S276 S297 T29 T125 Y86 Y211	N332	EF hand calcium-binding signature: D176-L188	protein phosphatase 2A (PR72)	BLAST MOTIFS BLOCKS
27	184	S36 T105 S40 S70 T117 Y50	N62	Tyrosine phosphatase active site domain: L63-V118	MAP kinase phosphatase (X17C)	BLAST PROFILESCAN BLOCKS PRINTS MOTIFS

Polypeptide	Amino	Potential	Potential	Signature Sequence	Homologous	Analytical
SEQ ID NO:	Acid Residues	Phosphorylation Sites	Glycosylation Sites		sednences	Methods
28	367	S10 S21 S44 S103 T116 T267 T309 S191 S213	N16 N17		protein phosphatase 2A, A-subunit	BLAST
		S218 S256 T305 S352 Y159 Y344				
29	118	S34 S84	N43	Signal peptide:	tyrosine	SPScan
				M1-A27	phosphatase	PFAM
				PDZ domain: H8-S73		BLAST
30	356	S9 S94 T209	N333	tyrosine-specific	tyrosine	PROFILESCAN
		T220 S259 S337		protein phosphatase	phosphatase	MOTIFS
		S5 S26 S75 S121		active site:	(myotubularin)	BLOCKS
		$\sim$		I108-K164		PRINTS
		S339 Y15 Y84				BLAST
31	453	S38 S73 S119	N43 N67 N357	protein phosphatase 2A	protein	PFAM
		S131 S193 S200		p55 subunit:	phosphatase 2A	MOTIFS
		T236 S293 S341		P10-K451	p55 regulatory	BLOCKS
		T379 T124 S173			subunit, alpha	PRINTS
		T214 S252 T256			isoform	BLAST
		S282 S302 S313				
		S391 S397				

### TABLE 3

Nucleotide   Tissue Expression   Disease or Condition   Vector				
Hematopoietic/Immune (0.333)   Inflammation (0.500)	Nucleotide SEQ ID NO:		Disease or Condition (Fraction of Total)	Vector
Nervous (0.216)	32	4	Cell proliferation (0.500) Inflammation (0.333)	PBLUESCRIPT
Reproductive (0.293)	33	Nervous (0.216) Reproductive(0.235) Cardiovascular (0.118)	Cell proliferation (0.530) Inflammation (0.352)	pINCY
Reproductive (0.284)	34	Reproductive (0.293) Gastrointestinal (0.192)	Cell proliferation (0.641) Inflammation (0.335)	pINCY
Nervous (0.529) Developmental (0.118)  (0.118) Gastrointestinal (0.118)  Hematopoietic/Immune (0.268)  Reproductive (0.244) Nervous (0.122)  Reproductive (0.440)  Hematopoietic/Immune (0.160) Nervous (0.150)  Cardiovascular (0.312) Reproductive (0.160)  Cardiovascular (0.312) Reproductive (0.153)  Cardiovascular (0.131) Reproductive (0.133)  Nervous (0.400) Gastrointestinal (0.133)  Gastrointestinal (0.267) Nervous (0.167)  Call proliferation (0.133)  Inflammation (0.133)  Inflammation (0.533)  Cell proliferation (0.733)  Neurological (0.133)  Inflammation (0.533)  Inflammation (0.533)	35	Reproductive (0.284) Nervous (0.210) Cardiovascular (0.1213)	Cell proliferation (0.729) Inflammation (0.272)	pINCY
Hematopoietic/Immune (0.268) Reproductive (0.244) Nervous (0.122) Reproductive (0.400) Hematopoietic/Immune (0.160) Nervous (0.160) Cardiovascular (0.312) Reproductive (0.312) Developmental (0.188) Nervous (0.400) Gastrointestinal (0.267) Developmental (0.133) Gastrointestinal (0.267) Nervous (0.233) Reproductive (0.167) Cell proliferation (0.533) Inflammation (0.533) (0.233) Reproductive (0.167) Cell proliferation (0.533)	36	ro l	Cell proliferation (0.588) Neurological (0.118) Inflammation (0.118)	pINCY
Reproductive (0.400) Hematopoietic/Immune (0.160) Nervous (0.160)  Cardiovascular (0.312) Reproductive (Cell proliferation (0.938) (0.312) Developmental (0.188)  Nervous (0.400) Gastrointestinal (0.267) Developmental (0.133)  Gastrointestinal (0.267) Nervous (0.233) Reproductive (0.167)  Cell proliferation (0.533)  Cell proliferation (0.533)  Cell proliferation (0.533)  Cell proliferation (0.533)	37	Hematopoietic/Immune (0.268) Reproductive (0.244) Nervous (0.122)		PBLUESCRIPT
Cardiovascular (0.312) Reproductive (ell proliferation (0.938)  (0.312) Developmental (0.188) Inflammation (0.125)  Nervous (0.400) Gastrointestinal (0.133) Reproductive (0.167) Nervous (0.267) Nervous (0.233) Reproductive (0.167) Cell proliferation (0.533)	38	Reproductive (0.400) Hematopoietic/Immune (0.160) Nervous (0.160)	Cell proliferation (0.600) Inflammation (0.320)	pINCY
Nervous (0.400) Gastrointestinal (0.267) Developmental (0.133)  Gastrointestinal (0.267) Nervous (0.233) Reproductive (0.167)  Cell proliferation (0.733)  Inflammation (0.133)  Cell proliferation (0.733)	39	Cardiovascular (0.312) Reproductive (0.312) Developmental (0.188)	Cell proliferation (0.938) Inflammation (0.125)	pINCY
Gastrointestinal (0.267) Nervous Inflammation (0.533) (0.233) Reproductive (0.167) Cell proliferation (0.534)	40	ST	Cell proliferation (0.733) Neurological (0.133) Inflammation (0.133)	pINCY
	41	Gastrointestinal (0.267) Nervous (0.233) Reproductive (0.167)	Inflammation (0.533) Cell proliferation (0.534)	pSPORT1

### Table 3 cont.

Nucleotide SEQ ID NO:	Tissue Expression (Fraction of Total)	Disease or Condition (Fraction of Total)	Vector
42	Musculoskeletal (0.500) Developmental (0.167) Gastrointestinal (0.167)	Cancer (0.834) Inflammation (0.167)	PBLUESCRIPT
43	Reproductive (0.240) Nervous (0.151) Gastrointestinal (0.135)	Cell proliferation (0.536) Inflammation (0.417)	pSPORT1
44	Hematopoietic/Immune (0.278) Nervous (0.222) Dermatologic (0.111)	Cell proliferation (0.444) Inflammation (0.389)	pINCY
45	Hematopoietic/Immune (0.500) Gastrointestinal (0.125) Nervous (0.125)	Inflammation (0.500) Cell proliferative (0.500)	PBLUESCRIPT
46	Nervous (0.220) Reproductive (0.213) Hematopoietic/Immune (0.140)	Cell proliferation (0.573) Inflammation (0.380)	pSPORT1
47	Hematopoietic/Immune (0.190) Gastrointestinal (0.165) Nervous (0.139)	Cell proliferation (0.582) Inflammation (0.354)	pSPORT1

Table 3 cont.

Nucleotide SEQ ID NO:	Tissue Expression (Fraction of Total)	Disease or Condition (Fraction of Total)	Vector
48	Nervous (0.333) Reproductive (0.333) Hematopoietic/Immune (0.111)	Cancer (0.444) Inflammation (0.222) Neurological (0.111)	PBLUESCRIPT
49	Nervous (0.724) Cardiovascular (0.103)	Inflammation (0.276) Cancer (0.241) Neurological (0.172)	pINCY
50	Reproductive (0.235) Hematopoietic/Immune (0.188) Gastrointestinal (0.129)	Cancer (0.447) Inflammation (0.282) Fetal (0.153)	pincy
51	Nervous (0.368) Developmental (0.158) Gastrointestinal (0.105)	Cancer (0.368) Fetal (0.211) Inflammation (0.105)	pSPORT1
52	Cardiovascular (0.312) Hematopoietic/Immune (0.312) Reproductive (0.158)	Fetal (0.688) Cancer (0.421) Inflammation (0.125)	pincy
53	Reproductive (0.412) Nervous (0.235) Developmental (0.118)	Cancer (0.471) Fetal (0.235) Inflammation (0.235)	pINCY
54	Nervous (0.714) Cardiovascular (0.107)	Cancer (0.250) Inflammation (0.250) Neurological (0.179)	pincy

Table 3 cont.

Nucleotide SEQ ID NO:	Tissue Expression (Fraction of Total)	Disease or Condition (Fraction of Total)	PBLUESCRIPT
55	Reproductive (0.533) Nervous (0.133)	Cell proliferation (0.601) Inflammation (0.270)	PBLUESCRIPT
99	<pre>Hematopoietic/Immune (0.278) Nervous (0.222) Reproductive (0.154)</pre>	Cell proliferation (0.388) Inflammation (0.333) Neurological (0.111)	PBLUESCRIPT
57	Hematopoietic/Immune (0.211) Cardiovascular (0.193) Nervous (0.175)	Cell proliferation (0.474) Inflammation (0.491)	PBLUESCRIPT
58	Reproductive (0.286) Cardiovascular (0.229) Musculoskeletal (0.143)	Cell proliferation (0.715) Inflammation (0.200)	pINCY
59	Reproductive (0.253) Gastrointestinal (0.211) Nervous (0.147)	Cancer and Cell proliferation (0.684) Inflammation and Immune Response (0.242)	psPORT1
90	Nervous (0.667) Reproductive (0.333)	Cancer (1.000)	pSPORT1
61	Reproductive (0.357) Cardiovascular (0.179) Nervous (0.125)	Cancer and Cell proliferation (0.642) Inflammation and Immune Response (0.232)	pSPORT1
62	Nervous (0.228) Reproductive (0.175) Cardiovascular (0.158) Hematopoietic/Immune (0.158)	Cancer (0.368) Inflammation and Immune Response (0.263) Fetal (0.211)	pINCY

### TABLE 4

Polynucleotide SEQ ID NO:	Library	Library Comment
32	BMARNOT02	Library was constructed using RNA isolated from the bone marrow of 24 male and female Caucasian donors, 16 to 70 years old.
33	SININOT01	Library was constructed using RNA isolated from ileum tissue removed from the small intestine of a 4-year-old Caucasian female, who died from a closed head injury. Patient history included jaundice as a baby. Previous surgeries included a double hernia repair
34	SPLNFET02	Library was constructed using RNA isolated from spleen tissue removed from a Caucasian male fetus, who died at 23 weeks' gestation from premature birth. Family history included diabetes.
35	OVARTUT02	Library was constructed using RNA isolated from ovarian tumor tissue removed from a 51-year-old Caucasian female during an exploratory laparotomy, total abdominal hysterectomy, salpingo-oophorectomy, and an incidental appendectomy. Pathology indicated mucinous cystadenoma presenting as a multiloculated neoplasm involving the entire left ovary. The right ovary contained a follicular cyst and a hemorrhagic corpus luteum. The uterus showed proliferative endometrium and a single intramural leiomyoma. The peritoneal biopsy indicated benign glandular inclusions consistent with endosalpingiosis. The patient presented with abnormal weight gain and ascites. Patient history included depressive disorder, joint pain, allergies, alcohol use, and a normal delivery. Family history included atherosclerotic coronary artery disease, benign hypertension, breast cancer and uterine cancer.

Polynucleotide	1 2	
SEQ ID NO:	LIDIALY	LIDIALY COMMENT
36	PANCTUT01	library was constructed using RNA isolated from pancreatic tumor tissue removed from a 65-year-old Caucasian female during radical subtotal pancreatectomy. Pathology indicated an invasive grade 2 adenocarcinoma. Patient history included type II diabetes, osteoarthritis, cardiovascular disease, and benign neoplasm in the large bowel. Previous surgeries included a total splenectomy, cholecystectomy, and abdominal hysterectomy. Family history included cardiovascular disease, type II diabetes, and stomach cancer.
37	SMCBUNT01	library was constructed using RNA isolated from bronchial smooth muscle cell tissue removed from a 21-year-old Caucasian male.
38	UTRSTUT05	Library was constructed using RNA isolated from uterine tumor tissue removed from a 41-year-old Caucasian female during a vaginal hysterectomy with dilation and curettage. Pathology indicated uterine leiomyoma. The endometrium was secretory and contained fragments of endometrial polyps. Benign endo- and ectocervical mucosa were identified in the endocervix. Patient history included a ventral hernia and a benign ovarian neoplasm.
39	UTRSTUT04	library was constructed using RNA isolated from uterine tumor tissue removed from a 34-year-old Caucasian female during a hysteroscopy and an exploratory laparotomy with dilation and curettage. Pathology indicated an endometrial polyp, subserosal leiomyoma, and fragments of leiomyoma. Family history included hyperlipidemia, depressive disorder, benign hypertension, cerebrovascular disease, arteriosclerotic cardiovascular disease, and type II diabetes.

### TABLE 4 cont

		11	17-		es ry	
I ABLE 4 cont.	Library Comment	structed using RNA	library was constructed using RNA isolated from the adrenal tissue of a 1	isolated from	library was constructed using RNA isolated from breast tumor tissue removed from a 55-year-old Caucasian female during a unilateral extended simple mastectomy. Pathology indicated invasive grade 4 mammary adenocarcinoma of tumor was identified in the deep dermis near the lactiferous ducts with extracapsular extension. Seven mid and low and five high axillary lymph nodes characterized by apocrine metaplasia, sclerosing adenosis, cyst formation, tachycardia, blood in the stool, and a benign breast neoplasm. Family history cerebrovascular disease, and depressive disorder.  library was constructed using RNA isolated from the lung tissue of a caucasian male fetus who died at 23 weeks' gestation.	from the umbilical cord blood of 12 individuals. The cells obtained 12 days with IL-5 before RNA was isolated from the cells were cultured for
	Library	SMCBUNT01	ADRENOT03	TESTNOT04	BRSTTUT01 LUNGNOT10	10100000
	Polynucleotide SEQ ID NO:	40	41	42	43	

Polynucleotide SEQ ID NO:	Library	Library Comment
46	BRST-TUT03	library was constructed using RNA isolated from breast tumor tissue removed from a 58-year-old Caucasian female during a unilateral extended simple mastectomy. Pathology indicated multicentric invasive grade 4 lobular carcinoma. The mass was identified in the upper outer quadrant, and three separate nodules were found in the lower outer quadrant of the left breast. Patient history included skin cancer, rheumatic heart disease, osteoarthritis, and tuberculosis. Family history included cerebrovascular disease, coronary artery aneurysm, breast cancer, prostate cancer, atherosclerotic coronary artery disease, and type I diabetes.
47	BRSTNOT05	library was constructed using RNA isolated from breast tissue removed from a 58-year-old Caucasian female during a unilateral extended simple mastectomy. Pathology for the associated tumor tissue indicated multicentric invasive grade 4 lobular carcinoma. Patient history included skin cancer, rheumatic heart disease, osteoarthritis, and tuberculosis. Family history included cerebrovascular and cardiovascular disease, breast and prostate cancer, and type I diabetes.

Polynucleotide SEQ ID NO:	Library	Library Comment
φ 9	SPLANOT02	The library was constructed using RNA isolated from the spleen tissue of a 29-year-old Caucasian male, who died from head trauma. Serologies were positive for cytomegalovirus (CMV). Patient history included alcohol, marijuana, and tobacco use.
49	BRAITUT08	The library was constructed using RNA isolated from brain tumor tissue removed from the left frontal lobe of a 47-year-old Caucasian male during excision of cerebral meningeal tissue. Pathology indicated grade 4 fibrillary astrocytoma with focal tumoral radionecrosis. Patient history included cerebrovascular disease, deficiency anemia, hyperlipidemia, epilepsy, and tobacco use. Family history included cerebrovascular disease and a malignant prostate neoplasm.
50	PANCTUT01	The library was constructed using RNA isolated from pancreatic tumor tissue removed from a 65-year-old Caucasian female during radical subtotal pancreatectomy. Pathology indicated an invasive grade 2 adenocarcinoma. Patient history included type II diabetes, osteoarthritis, cardiovascular disease, benign neoplasm in the large bowel, and a cataract. Previous surgeries included a total splenectomy, cholecystectomy, and abdominal hysterectomy. Family history included cardiovascular disease, type II diabetes, and stomach cancer.
51	BRAITUT02	The library was constructed using RNA isolated from brain tumor tissue removed from the frontal lobe of a 58-year-old Caucasian male during excision of a cerebral meningeal lesion. Pathology indicated a grade 2 metastatic hypernephroma. Patient history included a grade 2 renal cell carcinoma, insomnia, and chronic airway obstruction. Family history included a malignant neoplasm of the kidney.

# TABLE 4 cont.

Polynucleotide SEQ ID NO:	Library	Library Comment
52	THP1NOT03	The library was constructed using RNA isolated from untreated THP-1 cells. THP-1 (ATCC TIB 202) is a human promonocyte line derived from the peripheral blood of a 1-year-old Caucasian male with acute monocytic leukemia (ref: Int. J. Cancer (1980) 26:171).
53	BRSTNOT12	The library was constructed using RNA isolated from diseased breast tissue removed from a 32-year-old Caucasian female during a bilateral reduction mammoplasty. Pathology indicated nonproliferative fibrocystic disease. Family history included cardiovascular disease.
54	MUSCNOT07	The library was constructed using RNA isolated from muscle tissue removed from the forearm of a 38-year-old Caucasian female during a soft tissue excision. Pathology for the associated tumor tissue indicated intramuscular hemangioma. Family history included breast cancer, benign hypertension, cerebrovascular disease, colon cancer, and type II diabetes.
55	HUVESTB01	Library was constructed using RNA isolated from shear-stressed HUV-EC-C (ATCC CRL 1730) cells. HUV-EC-C is an endothelial cell line derived from the vein of a normal human umbilical cord (ref:PNAS 81:6413).
56	THYMNOT02	ibrary was constructed using polyA RNA isolated from thymus tissue removed from a 3-year-old Caucasian male, who died from drowning.
57	CARDNOT01	Library was constructed using RNA isolated from the cardiac muscle of a 65-year-old Caucasian male, who died from a self-inflicted gunshot wound.

# TABLE 4 cont.

Polynucleotide SEQ ID NO:	Library	Library Comment
5.8	UTRSNOT12	Library was constructed using RNA isolated from uterine myometrial tissue removed from a 41-year-old Caucasian female during a vaginal hysterectomy with a dilatation and curettage. The endometrium was secretory and contained fragments of endometrial polyps. Benign endo- and ectocervical mucosa were identified in the endocervix. Pathology for the associated tumor tissue indicated uterine leiomyoma. The patient presented with an unspecified menstrual disorder. Patient history included ventral hernia, normal delivery, a benign ovarian neoplasm, and tobacco abuse. Previous surgeries included a bilateral destruction of fallopian tubes, removal of a solitary ovary, and an exploratory laparotomy.
65	BEPINOT01	Library was constructed using RNA isolated from a bronchial epithelium primary cell line derived from a 54-year-old Caucasian male.
09	PGANNOT01	Library was constructed using RNA isolated from paraganglionic tumor tissue removed from the intra-abdominal region of a 46-year-old Caucasian male during exploratory laparotomy. Pathology indicated a benign paraganglioma and association with a grade 2 renal cell carcinoma, clear cell type.
61	BEPINOT01	Library was constructed using RNA isolated from a bronchial epithelium primary cell line derived from a 54-year-old Caucasian male.
62	DRGLNOT01	Library was constructed using RNA isolated from dorsal root ganglion tissue removed from the low thoracic/high lumbar region of a 32-year- old Caucasian male who died from acute pulmonary edema and bronchopneumonia, bilateral pleural and pericardial effusions, and malignant lymphoma (natural killer cell type). Patient history included probable cytomegalovirus infection, hepatic congestion and steatosis, splenomegaly, hemorrhagic cystitis, thyroid hemorrhage, and Bell's palsy.

#### Table 5

_	Program	Description	Reference	Parameter Threshold
	ABI FACTURA	A program that removes vector sequences and masks ambiguous bases in nucleic acid sequences.	Perkin-Elmer Applied Biosystems, Foster City, CA.	
•	ABI/PARACEL FDF	A Fast Data Finder useful in comparing and annotating amino acid or nucleic acid sequences.	Perkin-Elmer Applied Biosystems, Foster City, CA; Paracel Inc., Pasadena, CA.	Mismatch <50%
`	ABI AutoAssembler	A program that assembles nucleic acid sequences.	Perkin-Elmer Applied Biosystems, Foster City, CA.	
<b>-</b> 73-	BLAST	A Basic Local Alignment Search Tool useful in sequence similarity search for amino acid and nucleic acid sequences. BLAST includes five functions: blastp, blastn, blastx, tblastn, and tblastx.	Altschul, S.F. et al. (1990) J. Mol. Biol. 215:403-410; Altschul, S.F. et al. (1997) Nucleic Acids Res. 25: 3389-3402.	ESTs: Probability value= 1.0E-8 or less Full Length sequences: Probability value= 1.0E-10 or less
	FASTA	A Pearson and Lipman algorithm that searches for similarity between a query sequence and a group of sequences of the same type. FASTA comprises as least five functions: fasta, tfasta, fastx, tfastx, and ssearch.	Pearson, W.R. and D.J. Lipman (1988) Proc. Natl. Acad Sci. 85:2444-2448; Pearson, W.R. (1990) Methods Enzymol. 183: 63-98; and Smith, T.F. and M. S. Waterman (1981) Adv. Appl. Math. 2:482-489.	ESTs: fasta E value=1.06E-6 Assembled ESTs: fasta Identity= 95% or greater and Match length=200 bases or greater; fastx E value=1.0E-8 or less Full Length sequences: fastx score=100 or greater
<u></u>	вым <b>р</b> ѕ	A BLocks IMProved Searcher that matches a sequence against those in BLOCKS, PRINTS, DOMO, PRODOM, and PFAM databases to search for gene families, sequence homology, and structural fingerprint regions.	Henikoff, S and J.G. Henikoff, Nucl. Acid Res., 19:6565-72, 1991. J.G. Henikoff and S. Henikoff (1996) Methods Enzymol. 266:88- 105, and Attwood, T.K. et al. (1997) J. Chem. Inf. Comput. Sci. 37: 417-424.	Score=1000 or greater; Ratio of Score/Strength = 0.75 or larger; and, if applicable, Probability value= 1.0E-3 or less
<u></u>	нммек	An algorithm for searching a query sequence against hidden Markov model (HMM)-based databases of protein family consensus sequences, such as PFAM.	Krogh, A. et al. (1994) J. Mol. Biol., 235:1501-1531; Sonnhammer, E.L.L. et al. (1988) Nucleic Acids Res. 26:320-322.	Score=10-50 bits for PFAM hits, depending on individual protein families

### Table 5 (cont.)

Parameter Threshold	Normalized quality score CCG-specified "HIGH" value for that particular Prosite motif. Generally, score=1.4-2.1.		Score= 120 or greater, Match length= 56 or greater		Score=3.5 or greater	
Reference	Gribskov, M. et al. (1988) CABIOS 4:61-66; Gribskov, et al. (1989) Methods Enzymol. 183:146-159; Bairoch, A. et al. (1997) Nucleic Acids Res. 25: 217-221.	Ewing, B. et al. (1998) Genome Res. 8:175-185; Ewing, B. and P. Green (1998) Genome Res. 8:186- 194.	Smith, T.F. and M. S. Waterman (1981) Adv. Appl. Math. 2:482-489; Smith, T.F. and M. S. Waterman (1981) J. Mol. Biol. 147:195-197; and Green, P., University of Washington, Seattle, WA.	Gordon, D. et al. (1998) Genome Res. 8:195-202.	Nielson, H. et al. (1997) Protein Engineering 10:1-6; Claverie, J.M. and S. Audic (1997) CABIOS 12: 431-439.	Bairoch et al. <u>supra;</u> Wisconsin Package Program Manual, version 9, page M51-59, Genetics Computer Group, Madison, W1.
Description	An algorithm that searches for structural and sequence motifs in protein sequences that match sequence patterns defined in Prosite.	A base-calling algorithm that examines automated sequencer traces with high sensitivity and probability.	A Phils Revised Assembly Program including SWAT and CrossMatch, programs based on efficient implementation of the Smith-Waterman algorithm, useful in searching sequence homology and assembling DNA sequences.	A graphical tool for viewing and editing Phrap assemblies	A weight matrix analysis program that scans protein sequences for the presence of secretory signal peptides.	A program that searches amino acid sequences for pattems that matched those defined in Prosite.
Program	ProfileScan	Phred	<b>derif</b> d -74-	Consed	SPScan	Motifs



15

30

- 1. A substantially purified polypeptide comprising an amino acid sequence selected from the group consisting of SEQ ID NO:1-31, and fragments thereof.
- 5 2. A substantially purified variant having at least 90% amino acid sequence identity to the amino acid sequence of claim 1.
  - 3. An isolated and purified polynucleotide encoding the polypeptide of claim 1.
  - 4. An isolated and purified polynucleotide variant having at least 80% polynucleotide sequence identity to the polynucleotide of claim 3.
- 5. An isolated and purified polynucleotide which hybridizes under stringent conditions to the polynucleotide of claim 3.
  - 6. An isolated and purified polynucleotide having a sequence which is complementary to the polynucleotide of claim 3.
    - 7. A method for detecting a polynucleotide, the method comprising the steps of:
  - (a) hybridizing the polynucleotide of claim 6 to at least one nucleic acid in a sample, thereby forming a hybridization complex; and
    - (b) detecting the hybridization complex, wherein the presence of the hybridization complex correlates with the presence of the polynucleotide in the sample.
- 8. The method of claim 7 further comprising amplifying the polynucleotide prior to hybridization.
  - 9. An isolated and purified polynucleotide comprising a polynucleotide sequence selected from the group consisting of SEQ ID NO:32-62 and fragments thereof.
  - 10. An isolated and purified polynucleotide variant having at least 80% polynucleotide sequence identity to the polynucleotide of claim 9.
- 25 11. An isolated and purified polynucleotide having a sequence which is complementary to the polynucleotide of claim 9.
  - 12. An expression vector comprising at least a fragment of the polynucleotide of claim3.
    - 13. A host cell comprising the expression vector of claim 12.
    - 14. A method for producing a polypeptide, the method comprising the steps of:
      - a) culturing the host cell of claim 13 under conditions suitable for the expression of the polypeptide; and
        - b) recovering the polypeptide from the host cell culture.
- 15. A pharmaceutical composition comprising the polypeptide of claim 1 in conjunction35 with a suitable pharmaceutical carrier.
  - 16. A purified antibody which specifically binds to the polypeptide of claim 1.

#### WO 00/06728



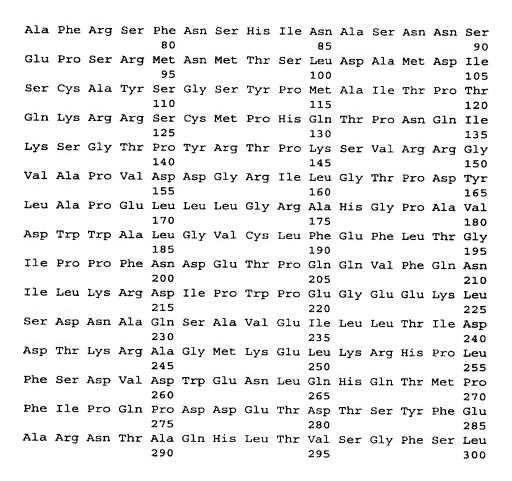
- 17. A purified agonist of the polypeptide of claim 1.
- 18. A purified antagonist of the polypeptide of claim 1.
- 19. A method for treating or preventing a disorder associated with decreased expression or activity of PHSP, the method comprising administering to a subject in need of such treatment an
   5 effective amount of the pharmaceutical composition of claim 15.
  - 20. A method for treating or preventing a disorder associated with increased expression or activity of PHSP, the method comprising administering to a subject in need of such treatment an effective amount of the antagonist of claim 18.

#### SEQUENCE LISTING

<110> INYCTE PHARMACEUTICALS, INC. HILLMAN, Jennifer L. LAL, Preeti TANG, Y. Tom CORLEY, Neil C. GUEGLER, Karl J. BAUGHN, Mariah R. PATTERSON, Chandra BANDMAN, Olga AU-YOUNG, Janice GORGONE, Gina A. YUE, Henry AZIMZAI, Yalda REDDY, Roopa LU, Dyung Aina M. SHIH, Leo L. <120> PHOSPHORYLATION EFFECTORS <130> PF-0565 PCT

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<221> misc\_feature

<223> Incyte Clone Number: 2197671

Met Ala His Ser Pro Val Gln Ser Gly Leu Pro Gly Met Gln Asn Leu Lys Ala Asp Pro Glu Glu Leu Phe Thr Lys Leu Glu Lys Ile Gly Lys Gly Ser Phe Gly Glu Val Phe Lys Gly Ile Asp Asn Arg Thr Gln Lys Val Val Ala Ile Lys Ile Ile Asp Leu Glu Glu Ala Glu Asp Glu Ile Glu Asp Ile Gln Gln Glu Ile Thr Val Leu Ser Gln Cys Asp Ser Pro Tyr Val Thr Lys Tyr Tyr Gly Ser Tyr Leu Lys Asp Thr Lys Leu Trp Ile Ile Met Glu Tyr Leu Gly Gly 100 Ser Ala Leu Asp Leu Leu Glu Pro Gly Arg Leu Asp Glu Thr Gln 110 115 Ile Ala Thr Ile Leu Arg Glu Ile Leu Lys Gly Leu Asp Tyr Leu 125 130 His Ser Glu Lys Lys Ile His Arg Asp Ile Lys Ala Ala Asn Val 145 Leu Leu Ser Glu His Gly Glu Val Lys Leu Ala Asp Phe Gly Val 155 160 Ala Gly Gln Leu Thr Asp Thr Gln Ile Lys Arg Asn Thr Phe Val 170 175 Gly Thr Pro Phe Trp Met Ala Pro Glu Val Ile Lys Gln Ser Ala 185 190 Tyr Asp Ser Lys Ala Asp Ile Trp Ser Leu Gly Ile Thr Ala Ile 200 205 Glu Leu Ala Arg Gly Glu Pro Pro His Ser Glu Leu His Pro Met 215 220 Lys Val Leu Phe Leu Ile Pro Lys Asn Asn Pro Pro Thr Leu Glu 230 235 Gly Asn Tyr Ser Lys Pro Leu Lys Glu Phe Val Glu Ala Cys Leu 245 Asn Lys Glu Pro Ser Phe Arg Pro Thr Ala Lys Glu Leu Leu Lys 265 His Lys Phe Ile Leu Arg Asn Ala Lys Lys Thr Ser Tyr Leu Thr 275 280

```
Glu Leu Ile Asp Arg Tyr Lys Arg Trp Lys Ala Glu Gln Ser His
                290
                                    295
Asp Asp Ser Ser Ser Glu Asp Ser Asp Ala Glu Thr Asp Gly Gln
                305
                                    310
Ala Ser Gly Gly Ser Asp Ser Gly Asp Trp Ile Phe Thr Ile Arg
                                    325
Glu Lys Asp Pro Lys Asn Leu Glu Asn Gly Ala Leu Gln Pro Ser
                335
                                    340
Asp Leu Asp Arg Asn Lys Met Lys Asp Ile Pro Lys Arg Pro Phe
                350
Ser Gln Cys Leu Ser Thr Ile Ile Ser Pro Leu Phe Ala Glu Leu
                                    370
Lys Glu Lys Ser Gln Ala Cys Gly Gly Asn Leu Gly Ser Ile Glu
                380
                                    385
Glu Leu Arg Gly Ala Ile Tyr Leu Ala Glu Glu Ala Cys Pro Gly
                395
                                    400
Ile Ser Asp Thr Met Val Ala Gln Leu Val Gln Arg Leu Gln Arg
                410
                                    415
Tyr Ser Leu Ser Gly Gly Gly Thr Ser Ser His
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<210> 4

<211> 218

<212> PRT

<213> Homo sapiens

<220>

<221> misc\_feature

<223> Incyte Clone Number: 2594943

<400> 4

Met Asn Cys Arg Ser Glu Val Leu Glu Val Ser Val Glu Gly Arg Gln Val Glu Glu Ala Met Leu Ala Val Leu His Thr Val Leu Leu His Arg Ser Thr Gly Lys Phe His Tyr Lys Lys Glu Gly Thr Tyr Ser Ile Gly Thr Val Gly Thr Gln Asp Val Asp Cys Asp Phe Ile Asp Phe Thr Tyr Val Arg Val Ser Ser Glu Glu Leu Asp Arg Ala Leu Arg Lys Val Val Gly Glu Phe Lys Asp Ala Leu Arg Asn Ser 85 Gly Gly Asp Gly Leu Gly Gln Met Ser Leu Glu Phe Tyr Gln Lys 95 100 Lys Lys Ser Arg Trp Pro Phe Ser Asp Glu Cys Ile Pro Trp Glu 110 115 Val Trp Thr Val Lys Val His Val Val Ala Leu Ala Thr Glu Gln 125 130 Glu Arg Gln Ile Cys Arg Glu Lys Val Gly Glu Lys Leu Cys Glu 140 145 Lys Ile Ile Asn Ile Val Glu Val Met Asn Arg His Glu Tyr Leu 155 160 Pro Lys Met Pro Thr Gln Ser Glu Val Asp Asn Val Phe Asp Thr 170 175 180

Gly Leu Arg Asp Val Gln Pro Tyr Leu Tyr Lys Ile Ser Phe Gln
185 - 185 - 190 - 190 - 195

Ile Thr Asp Ala Leu Gly Thr Ser Val Thr Thr Thr Met Arg Arg
200 - 190 - 205 - 190 - 190

Leu Ile Lys Asp Thr Leu Ala Leu
215

<210> 5
<211> 474
<212> PRT
<213> Homo sapiens
<220>
<221> misc\_feature

<223> Incyte Clone Number: 1513871 <400> 5 Met Ile Met Asn Lys Met Lys Asn Phe Lys Arg Arg Phe Ser Leu 10 Ser Val Pro Arg Thr Glu Thr Ile Glu Glu Ser Leu Ala Glu Phe 20 25 Thr Glu Gln Phe Asn Gln Leu His Asn Arg Arg Asn Glu Asn Leu 35 Gln Leu Gly Pro Leu Gly Arg Asp Pro Pro Gln Glu Cys Ser Thr Phe Ser Pro Thr Asp Ser Gly Glu Glu Pro Gly Gln Leu Ser Pro 65 Gly Val Gln Phe Gln Arg Arg Gln Asn Gln Arg Arg Phe Ser Met 80 Glu Asp Val Ser Lys Arg Leu Ser Leu Pro Met Asp Ile Arg Leu 95 Pro Gln Glu Phe Leu Gln Lys Leu Gln Met Glu Ser Pro Asp Leu 115 Pro Lys Pro Leu Ser Arg Met Ser Arg Arg Ala Ser Leu Ser Asp 130 Ile Gly Phe Gly Lys Leu Glu Thr Tyr Val Lys Leu Asp Lys Leu 145 Gly Glu Gly Thr Tyr Ala Thr Val Phe Lys Gly Arg Ser Lys Leu 160 Thr Glu Asn Leu Val Ala Leu Lys Glu Ile Arg Leu Glu His Glu 175 Glu Gly Ala Pro Cys Thr Ala Ile Arg Glu Val Ser Leu Leu Lys 185 190 Asn Leu Lys His Ala Asn Ile Val Thr Leu His Asp Leu Ile His 200 205 Thr Asp Arg Ser Leu Thr Leu Val Phe Glu Tyr Leu Asp Ser Asp 215 220 Leu Lys Gln Tyr Leu Asp His Cys Gly Asn Leu Met Ser Met His 230 235 Asn Val Lys Ile Phe Met Phe Gln Leu Leu Arg Gly Leu Ala Tyr 245 250 Cys His His Arg Lys Ile Leu His Arg Asp Leu Lys Pro Gln Asn 260 265 Leu Leu Ile Asn Glu Arg Gly Glu Leu Lys Leu Ala Asp Phe Gly 275 280

Leu Ala Arg Ala Lys Ser Val Pro Thr Lys Thr Tyr Ser Asn Glu 290 295 Val Val Thr Leu Trp Tyr Arg Pro Pro Asp Val Leu Leu Gly Ser 305 310 Thr Glu Tyr Ser Thr Pro Ile Asp Met Trp Gly Val Gly Cys Ile His Tyr Glu Met Ala Thr Gly Arg Pro Leu Phe Pro Gly Ser Thr 340 Val Lys Glu Glu Leu His Leu Ile Phe Arg Leu Leu Gly Thr Pro Thr Glu Glu Thr Trp Pro Gly Val Thr Ala Phe Ser Glu Phe Arg 370 Thr Tyr Ser Phe Pro Cys Tyr Leu Pro Gln Pro Leu Ile Asn His 380 385 Ala Pro Arg Leu Asp Thr Asp Gly Ile His Leu Leu Ser Ser Leu 395 400 Leu Leu Tyr Glu Ser Lys Ser Arg Met Ser Ala Glu Ala Ala Leu 415 Ser His Ser Tyr Phe Arg Ser Leu Gly Glu Arg Val His Gln Leu 425 430 Glu Asp Thr Ala Ser Ile Phe Ser Leu Lys Glu Ile Gln Leu Gln 440 445 Lys Asp Pro Gly Tyr Arg Gly Leu Ala Phe Gln Gln Pro Gly Arg 455 460 Gly Lys Asn Arg Arg Gln Ser Ile Phe 470

<210> 6

<211> 540

<212> PRT

<213> Homo sapiens

<220>

<221> misc\_feature

<223> Incyte Clone Number: 156108

<400> 6

Met Asn Gly Glu Ala Ile Cys Ser Ala Leu Pro Thr Ile Pro Tyr His Lys Leu Ala Asp Leu Arg Tyr Leu Ser Arg Gly Ala Ser Gly Thr Val Ser Ser Ala Arg His Ala Asp Trp Arg Val Gln Val Ala 40 Val Lys His Leu His Ile His Thr Pro Leu Leu Asp Ser Glu Arg 50 Lys Asp Val Leu Arg Glu Ala Glu Ile Leu His Lys Ala Arg Phe Ser Tyr Ile Leu Pro Ile Leu Gly Ile Cys Asn Glu Pro Glu Phe 80 85 Leu Gly Ile Val Thr Glu Tyr Met Pro Asn Gly Ser Leu Asn Glu 95 100 Leu Leu His Arg Lys Thr Glu Tyr Pro Asp Val Ala Trp Pro Leu 110 115 Arg Phe Arg Ile Leu His Glu Ile Ala Leu Gly Val Asn Tyr Leu

				125					130					135
His	Asn	Met	Thr	Pro 140	Pro	Leu	Leu	His	His 145	Asp	Leu	Lys	Thr	Gln 150
Asn	Ile	Leu	Leu	Asp 155	Asn	Glu	Phe	His	Val 160	Lys	Ile	Ala	Asp	Phe 165
Gly	Leu	Ser	Lys	Trp 170	Arg	Met	Met	Ser	Leu 175	Ser	Gln	Ser	Arg	Ser 180
Ser	Lys	Ser	Ala	Pro 185	Glu	Gly	Gly	Thr		Ile	Tyr	Met	Pro	
Glu	Asn	Tyr	Glu	Pro 200	Gly	Gln	Lys	Ser		Ala	Ser	Ile	Lys	
Asp	Ile	Tyr	Ser	Tyr 215	Ala	Val	Ile	Thr	Trp 220	Glu	Val	Leu	Ser	
Lys	Gln	Pro	Phe	Glu 230	Asp	Val	Thr	Asn		Leu	Gln	Ile	Met	
Ser	Val	Ser	Gln		His	Arg	Pro	Val		Asn	Glu	Glu	Ser	
Pro	Tyr	Asp	Ile		His	Arg	Ala	Arg		Ile	Ser	Leu	Ile	
Ser	Gly	Trp	Ala	Gln 275	Asn	Pro	Asp	Glu		Pro	Ser	Phe	Leu	Lys 285
Cys	Leu	Ile	Glu	Leu 290	Glu	Pro	Val	Leu	Arg 295	Thr	Phe	Glu	Glu	Ile 300
Thr	Phe	Leu	Glu	Ala 305	Val	Ile	Gln	Leu	Lys 310	Lys	Thr	Lys	Leu	Gln 315
Ser	Val	Ser	Ser	Ala 320	Ile	His	Leu	Cys	Asp 325	Lys	Lys	Lys	Met	
Leu	Ser	Leu	Asn	Ile 335	Pro	Val	Asn	His	Gly 340	Pro	Gln	Glu	Glu	Ser 345
Cys	Gly	Ser	Ser	Gln 350	Leu	His	Glu	Asn	Ser 355	Gly	Ser	Pro	Glu	Thr 360
Ser	Arg	Ser	Leu	Pro 365	Ala	Pro	Gln	Asp	Asn 370	Asp	Phe	Leu	Ser	Arg 375
Lys	Ala	Gln	Asp	Cys 380	Tyr	Phe	Met	Lys	Leu 385	His	His	Cys	Pro	Gly 390
Asn	His	Ser	Trp	Asp 395	Ser	Thr	Ile	Ser	Gly 400	Ser	Gln	Arg	Ala	Ala 405
Phe	Cys	Asp	His	Lys 410	Thr	Thr	Pro	Cys	Ser 415	Ser	Ala	Ile	Ile	Asn 420
Pro	Leu	Ser	Thr	Ala 425	Gly	Asn	Ser	Glu	Arg 430	Leu	Gln	Pro	Gly	Ile 435
Ala	Gln	Gln	Trp	Ile 440	Gln	Ser	Lys	Arg	Glu 445	Asp	Ile	Val	Asn	Gln 450
Met	Thr	Glu	Ala	Cys 455	Leu	Asn	Gln	Ser	Leu 460	Asp	Ala	Leu	Leu	Ser 465
Arg	Asp	Leu	Ile	Met 470	Lys	Glu	Asp	Tyr	Glu 475	Leu	Val	Ser	Thr	Lys 480
Pro	Thr	Arg	Thr	Ser 485	Lys	Val	Arg	Gln		Leu	Asp	Thr	Thr	Asp 495
Ile	Gln	Gly	Glu	Glu 500	Phe	Ala	Lys	Val	Ile 505	Val	Gln	Lys	Leu	Lys 510
Asp	Asn	Lys	Gln	Met 515	Gly	Leu	Gln	Pro		Pro	Glu	Ile	Leu	
Val	Ser	Arg	Ser	Pro 530	Ser	Leu	Asn	Leu	Leu 535	Gln	Asn	Lys	Ser	Met 540

<210> 7

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<211> 454
<212> PRT
<213> Homo sapiens
<220>
<221> misc_feature
<223> Incyte Clone Number: 2883243
<400> 7
Met Tyr Asn Thr Val Trp Asn Met Glu Asp Leu Asp Leu Glu Tyr
Ala Lys Thr Asp Ile Asn Cys Gly Thr Asp Leu Met Phe Tyr Ile
                                     25
Glu Met Asp Pro Pro Ala Leu Pro Pro Lys Pro Pro Lys Pro Thr
                 35
                                     40
Thr Val Ala Asn Asn Gly Met Asn Asn Asn Met Ser Leu Gln Asp
                                     55
Ala Glu Trp Tyr Trp Gly Asp Ile Ser Arg Glu Glu Val Asn Glu
                                     70
Lys Leu Arg Asp Thr Ala Asp Gly Thr Phe Leu Val Arg Asp Ala
                 80
                                     85
Ser Thr Lys Met His Gly Asp Tyr Thr Leu Thr Leu Arq Lys Gly
                 95
                                    100
Gly Asn Asn Lys Leu Ile Lys Ile Phe His Arg Asp Gly Lys Tyr
                110
                                    115
Gly Phe Ser Asp Pro Leu Thr Phe Ser Ser Val Val Glu Leu Ile
                125
                                    130
Asn His Tyr Arg Asn Glu Ser Leu Ala Gln Tyr Asn Pro Lys Leu
                140
                                    145
Asp Val Lys Leu Leu Tyr Pro Val Ser Lys Tyr Gln Gln Asp Gln
Val Val Lys Glu Asp Asn Ile Glu Ala Val Gly Lys Lys Leu His
Glu Tyr Asn Thr Gln Phe Gln Glu Lys Ser Arg Glu Tyr Asp Arg
Leu Tyr Glu Glu Tyr Thr Arg Thr Ser Gln Glu Ile Gln Met Lys
Arg Thr Ala Ile Glu Ala Phe Asn Glu Thr Ile Lys Ile Phe Glu
Glu Gln Cys Gln Thr Gln Glu Arg Tyr Ser Lys Glu Tyr Ile Glu
                                    235
Lys Phe Lys Arg Glu Gly Asn Glu Lys Glu Ile Gln Arg Ile Met
                245
                                    250
His Asn Tyr Asp Lys Leu Lys Ser Arg Ile Ser Glu Ile Ile Asp
                260
                                    265
Ser Arg Arg Leu Glu Glu Asp Leu Lys Lys Gln Ala Ala Glu
                275
                                    280
Tyr Arg Glu Ile Asp Lys Arg Met Asn Ser Ile Lys Pro Asp Leu
                290
                                     295
                                                         300
Ile Gln Leu Arg Lys Thr Arg Asp Gln Tyr Leu Met Trp Leu Thr
                305
                                     310
Gln Lys Gly Val Arg Gln Lys Lys Leu Asn Glu Trp Leu Gly Asn
                320
                                     325
Glu Asn Thr Glu Asp Gln Tyr Ser Leu Val Glu Asp Asp Glu Asp
                335
                                     340
                                                         345
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Leu Pro His His Asp Glu Lys Thr Trp Asn Val Gly Ser Ser Asn 355 Arg Asn Lys Ala Glu Asn Leu Leu Arg Gly Lys Arg Asp Gly Thr 370 Phe Leu Val Arg Glu Ser Ser Lys Gln Gly Cys Tyr Ala Cys Ser 380 385 Val Val Val Asp Gly Glu Val Lys His Cys Val Ile Asn Lys Thr 395 400 Ala Thr Gly Tyr Gly Phe Ala Glu Pro Tyr Asn Leu Tyr Ser Ser 410 415 Leu Lys Glu Leu Val Leu His Tyr Gln His Thr Ser Leu Val Gln 425 430 His Asn Asp Ser Leu Asn Val Thr Leu Ala Tyr Pro Val Tyr Ala 440 Gln Gln Arg Arg

<210> 8

<211> 502

<212> PRT

<213> Homo sapiens

<220>

<221> misc\_feature

<223> Incyte Clone Number: 3173355

<400> 8

Met Phe Gly Thr Leu Leu Leu Tyr Cys Phe Phe Leu Ala Thr Val Pro Ala Leu Ala Glu Thr Gly Gly Glu Arg Gln Leu Ser Pro Glu Lys Ser Glu Ile Trp Gly Pro Gly Leu Lys Ala Asp Val Val Leu 35 40 Pro Ala Arg Tyr Phe Tyr Ile Gln Ala Val Asp Thr Ser Gly Asn 50 55 Lys Phe Thr Ser Ser Pro Gly Glu Lys Val Phe Gln Val Lys Val Ser Ala Pro Glu Glu Gln Phe Thr Arg Val Gly Val Gln Val Leu 85 Asp Arg Lys Asp Gly Ser Phe Ile Val Arg Tyr Arg Met Tyr Ala 95 100 Ser Tyr Lys Asn Leu Lys Val Glu Ile Lys Phe Gln Gly Gln His 110 115 Val Ala Lys Ser Pro Tyr Ile Leu Lys Gly Pro Val Tyr His Glu 125 130 Asn Cys Asp Cys Pro Leu Gln Asp Ser Ala Ala Trp Leu Arg Glu 140 145 Met Asn Cys Pro Glu Thr Ile Ala Gln Ile Gln Arg Asp Leu Ala 155 160 His Phe Pro Ala Val Asp Pro Glu Lys Ile Ala Val Glu Ile Pro 170 175 Lys Arg Phe Gly Gln Arg Gln Ser Leu Cys His Tyr Thr Leu Lys 190 Asp Asn Lys Val Tyr Ile Lys Thr His Gly Glu His Val Gly Phe 205 Arg Ile Phe Met Asp Ala Ile Leu Leu Ser Leu Thr Arg Lys Val

215

225

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Lys Met Pro Asp Val Glu Leu Phe Val Asn Leu Gly Asp Trp Pro
                230
                                     235
Leu Glu Lys Lys Lys Ser Asn Ser Asn Ile His Pro Ile Phe Ser
                245
                                     250
Trp Cys Gly Ser Thr Asp Ser Lys Asp Ile Val Met Pro Thr Tyr
                                     265
Asp Leu Thr Asp Ser Val Leu Glu Thr Met Gly Arg Val Ser Leu
                275
Asp Met Met Ser Val Gln Ala Asn Thr Gly Pro Pro Trp Glu Ser
                290
Lys Asn Ser Thr Ala Val Trp Arg Gly Arg Asp Ser Arg Lys Glu
                305
Arg Leu Glu Leu Val Lys Leu Ser Arg Lys His Pro Glu Leu Ile
                                     325
Asp Ala Ala Phe Thr Asn Phe Phe Phe Lys His Asp Glu Asn
                335
                                     340
Leu Tyr Gly Pro Ile Val Lys His Ile Ser Phe Phe Asp Phe Phe
                350
                                     355
Lys His Lys Tyr Gln Ile Asn Ile Asp Gly Thr Val Ala Ala Tyr
                365
                                     370
                                                         375
Arg Leu Pro Tyr Leu Leu Val Gly Asp Ser Val Val Leu Lys Gln
                380
                                    385
                                                         390
Asp Ser Ile Tyr Tyr Glu His Phe Tyr Asn Glu Leu Gln Pro Trp
                395
                                     400
                                                         405
Lys His Tyr Ile Pro Val Lys Ser Asn Leu Ser Asp Leu Leu Glu
                410
                                     415
Lys Leu Lys Trp Ala Lys Asp His Asp Glu Glu Ala Lys Lys Ile
                425
                                     430
Ala Lys Ala Gly Gln Glu Phe Ala Arg Asn Asn Leu Met Gly Asp
                440
                                     445
Asp Ile Phe Cys Tyr Tyr Phe Lys Leu Phe Gln Glu Tyr Ala Asn
                455
                                     460
Leu Gln Val Ser Glu Pro Gln Ile Arg Glu Gly Met Lys Arg Val
                470
                                     475
Glu Pro Gln Thr Glu Asp Asp Leu Phe Pro Cys Thr Cys His Arg
                485
Lys Lys Thr Lys Asp Glu Leu
<210> 9
<211> 282
<212> PRT
<213> Homo sapiens
<220>
<221> misc_feature
<223> Incyte Clone Number: 5116906
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Met Trp Ala Cys Gly Val Ile Leu Tyr Ile Leu Leu Val Gly Tyr
                                     10
Pro Pro Phe Trp Asp Glu Asp Gln His Arg Leu Tyr Gln Gln Ile
                 20
                                      25
Lys Ala Gly Ala Tyr Asp Phe Pro Ser Pro Glu Trp Asp Thr Val
                 35
                                      40
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220

Thr Pro Glu Ala Lys Asp Leu Ile Asn Lys Met Leu Thr Ile Asn 50 Pro Ala Lys Arg Ile Thr Ala Ser Glu Ala Leu Lys His Pro Trp 65 Ile Cys Gln Arg Ser Thr Val Ala Ser Met Met His Arg Gln Glu 80 85 Thr Val Asp Cys Leu Lys Lys Phe Asn Ala Arg Arg Lys Leu Lys 95 100 Gly Ala Ile Leu Thr Thr Met Leu Ala Thr Arg Asn Phe Ser Ala 110 115 Ala Lys Ser Leu Leu Lys Lys Pro Asp Gly Val Lys Glu Ser Thr 125 130 Glu Ser Ser Asn Thr Thr Ile Glu Asp Glu Asp Val Lys Ala Arg 140 145 Lys Gln Glu Ile Ile Lys Val Thr Glu Gln Leu Ile Glu Ala Ile 160 155 Asn Asn Gly Asp Phe Glu Ala Tyr Thr Lys Ile Cys Asp Pro Gly 175 Leu Thr Ala Phe Glu Pro Glu Ala Leu Gly Asn Leu Val Glu Gly 190 Met Asp Phe His Arg Phe Tyr Phe Glu Asn Ala Leu Ser Lys Ser 205 200 Asn Lys Pro Ile His Thr Ile Ile Leu Asn Pro His Val His Leu 220 Val Gly Asp Asp Ala Ala Cys Ile Ala Tyr Ile Arg Leu Thr Gln Tyr Met Asp Gly Ser Gly Met Pro Lys Thr Met Gln Ser Glu Glu 250 245 Thr Arg Val Trp His Arg Arg Asp Gly Lys Trp Gln Asn Val His 260 265 Phe His Arg Ser Gly Ser Pro Thr Val Pro Ile Asn 275

<210> 10

<211> 510

<212> PRT

<213> Homo sapiens

<220>

<221> misc\_feature

<223> Incyte Clone Number: 940589

<400> 10

 Met
 Lys
 Ala
 Asp
 Ile
 Lys
 Ile
 Trp
 Ile
 Leu
 Thr
 Gly
 Asp
 Lys
 Gln
 15

 Glu
 Thr
 Ala
 Ile
 Asn
 Ile
 Gly
 His
 Ser
 Cys
 Lys
 Leu
 Leu
 Lys
 Lys

 Asn
 Met
 Gly
 Met
 Ile
 Val
 Ile
 Asn
 Glu
 Gly
 Ser
 Leu
 Asp
 Ser
 Phe

 Ser
 Asn
 Thr
 Gln
 Asn
 Ser
 Arg
 Lys
 Glu
 Ala
 Val
 Leu
 Leu
 Ala
 Lys

 Ser
 Asn
 Thr
 Glu
 Asn
 Ile
 Val
 Ala
 Phe
 Lys
 Glu
 Ser
 Phe
 Glu
 Ala

 Met
 Lys
 His
 Pro
 Asn
 Ile
 Val
 Ala
 Phe
 Lys
 Glu
 Ser
 Phe
 Glu
 Ala

 Glu
 Gly
 His
 Leu
 Tyr
 Lys
 Met
 Glu
 Tyr
 Cy

T ou	Mot	<i>(</i> 125	T 110	<b>T</b> 1.0	T	~1 m	~1 ~	T	<b>~1</b>	T	T	Dh.a	D	<b>a</b> 1
Leu	Met	Gln	Lys	95	ьуs	GIII	GIII	ьys	100	гÀг	Leu	Pne	Pro	105
Asp	Met	Ile	Leu	Asn 110	Trp	Phe	Thr	Gln	Met 115	Cys	Leu	Gly	Val	Asn 120
His	Ile	His	Lys	Lys 125	Arg	Val	Leu	His		Asp	Ile	Lys	Ser	
Asn	Ile	Phe	Leu	Thr	Gln	Asn	Gly	Lys		Lys	Leu	Gly	Asp	
Gly	Ser	Ala	Arg		Leu	Ser	Asn	Pro		Ala	Phe	Ala	Cys	
Tyr	Val	Gly	Thr		Tyr	Tyr	Val	Pro		Glu	Ile	Trp	Glu	
Leu	Pro	Tyr	Asn		Lys	Ser	Asp	Ile		Ser	Leu	Gly	Cys	
Leu	Tyr	Glu	Leu		Thr	Leu	Lys	His		Phe	Gln	Ala	Asn	
Trp	Lys	Asn	Leu		Leu	Lys	Val	Cys		Gly	Cys	Ile	Ser	
Leu	Pro	Ser	His		Ser	Tyr	Glu	Leu		Phe	Leu	Val	Lys	
Met	Phe	Lys	Arg		Pro	Ser	His	Arg		Ser	Ala	Thr	Thr	
Leu	Ser	Arg	Gly		Val	Ala	Arg	Leu		Gln	Lys	Cys	Leu	
Pro	Glu	Ile	Ile		Glu	Tyr	Gly	Glu		Val	Leu	Glu	Glu	
Lys	Asn	Ser	Lys		Asn	Thr	Pro	Arg		Lys	Thr	Asn	Pro	
Arg	Ile	Arg	Ile		Leu	Gly	Asn	Glu		Ser	Thr	Val	Gln	
Glu	Glu	Gln	Asp		Lys	Gly	Ser	His		Asp	Leu	Glu	Ser	
Asn	Glu	Asn	Leu		Glu	Ser	Ala	Leu		Arg	Val	Asn	Arg	
Glu	Lys	Gly	Asn		Ser	Val	His	Leu		Lys	Ala	Ser	Ser	
Asn	Leu	His	Arg		Gln	Trp	Glu	Lys		Val	Pro	Asn	Thr	
Leu	Thr	Ala	Leu		Asn	Ala	Ser	Ile		Thr	Ser	Ser	Leu	
Ala	Glu	Asp	Asp		Gly	Gly	Ser	Val		Lys	Tyr	Ser	Lys	Asn 405
Thr	Thr	Arg	Lys		Trp	Leu	Lys	Glu		Pro	Asp	Thr	Leu	Leu 420
Asn	Ile	Leu	Lys		Ala	Asp	Leu	Ser		Ala	Phe	Gln	Thr	Tyr 435
Thr	Ile	Tyr	Arg		Gly	Ser	Glu	Gly		Leu	Lys	Gly	Pro	Leu 450
Ser	Glu	Glu	Thr		Ala	Ser	Asp	Ser		Asp	Gly	Gly	His	
Ser	Val	Ile	Leu		Pro	Glu	Arg	Leu		Pro	Gly	Leu	Asp	Glu 480
Glu	Asp	Thr	Asp		Glu	Glu	Glu	Asp			Pro	Asp	Trp	Val 495
Ser	Glu	Leu	Lys		Arg	Ala	Gly	Trp		Gly	Leu	Cys	Asp	Arg 510

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<210> 11
<211> 248
<212> PRT
<213> Homo sapiens
<220>
<221> misc feature
<223> Incyte Clone Number: 304421
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Thr Pro Cys Pro Ser Ile Leu Glu Leu Glu Glu Leu Leu Arg Ala
                 20
                                     25
Gly Lys Ser Ser Cys Ser Arg Val Asp Glu Val Trp Pro Asn Leu
                 35
Phe Ile Gly Asp Ala Met Asp Ser Leu Gln Lys Gln Asp Leu Arg
Arg Pro Lys Ile His Gly Ala Val Gln Ala Ser Pro Tyr Gln Pro
Pro Thr Leu Ala Ser Leu Gln Arg Leu Leu Trp Val Arg Gln Ala
Ala Thr Leu Asn His Ile Asp Glu Val Trp Pro Ser Leu Phe Leu
                                    100
Gly Asp Ala Tyr Ala Ala Arg Asp Lys Ser Lys Leu Ile Gln Leu
                                    115
Gly Ile Thr His Val Val Asn Ala Ala Ala Gly Lys Phe Gln Val
                125
                                    130
Asp Thr Gly Ala Lys Phe Tyr Arg Gly Met Ser Leu Glu Tyr Tyr
                140
                                    145
Gly Ile Glu Ala Asp Asp Asn Pro Phe Phe Asp Leu Ser Val Tyr
                                    160
Phe Leu Pro Val Ala Arg Tyr Ile Arg Ala Ala Leu Ser Val Pro
                170
                                    175
Gln Gly Arg Val Leu Val His Cys Ala Met Gly Val Ser Arg Ser
                185
                                    190
Ala Thr Leu Val Leu Ala Phe Leu Met Ile Tyr Glu Asn Met Thr
                200
                                    205
Leu Val Glu Ala Ile Gln Thr Val Gln Ala His Arg Asn Ile Cys
                215
                                    220
Pro Asn Ser Gly Phe Leu Arg Gln Leu Gln Val Leu Asp Asn Arg
                230
                                    235
Leu Gly Arg Glu Thr Gly Arg Phe
                245
<210> 12
<211> 810
<212> PRT
<213> Homo sapiens
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<220>

<221> misc\_feature

<223> Incyte Clone Number: 1213802

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		Lys		20					25					30
		Asn		35					40					45
		Gln		50					55			_	-	60
		Glu		65					70				_	75
		Leu		80					85					90
		Leu		95					100					105
		Ser		110					115					120
		Asn		125					130					135
		Val		140					145					150
		Pro		155					160					165
		Asp		170					175					180
		Gln		185					190					195
		Arg		200					205					210
		Gly Lys		215					220			_	_	225
		Leu		230					235			_		240
		Arg		245					250					255
		Glu		260					265					270
		Lys		275					280					285
		Leu		290					295					300
		Ile		305					310					315
		Glu		320					325					330
		Asp		335					340					345
		Glu		350					355					360
		Thr		365					370					375
		Ser		380					385					390
		Glu		395					400					405
							-10	_, 5		5				

				410					415					420
Glu	Arg	Gln	Lys	Ser 425	Lys	Lys	Asp	Thr	Thr 430	Cys	Ile	Lys	Leu	Lys 435
Ile	Asp	Ser	Glu	Ile 440	Lys	Lys	Thr	Val	Val 445	Leu	Pro	Pro	Ile	Val 450
Ala	Ser	Arg	Gly		Ser	Glu	Glu	Pro		Gly	Lys	Thr	Lys	
Met	Gln	Glu	Val		Ile	Lys	Thr	Leu	Glu	Glu	Ile	Lys	Leu	Glu
Lys	Ala	Leu	Arg	Val	Gln	Gln	Ser	Ser		Ser	Ser	Thr	Ser	
Pro	Ser	Gln	His		Ala	Thr	Pro	Gly		Arg	Arg	Leu	Leu	
Ile	Thr	Lys	Arg		Gly	Met	Lys	Glu		Lys	Asn	Leu	Gln	
Gly	Asn	Glu	Val		Ser	Gln	Ser	Ser		Arg	Thr	Glu	Ala	
Glu	Ala	ser	Gly		Thr	Thr	Gly	Val	535 Asp	Ile	Thr	Lys	Ile	540 Gln
Val	Lys	Arg	Cys	545 Glu	Thr	Met	Arg	Glu	550 Lys	His	Met	Gln	Lys	555 Gln
Gln	Glu	Arg	Glu	560 Lys	Ser	Val	Leu	Thr	565 Pro	Leu	Arg	Gly	Asp	570 Val
Ala	Ser	Cys	Asn	575 Thr	Gln	Val	Ala	Glu	580 Lys	Pro	Val	Leu	Thr	585 Ala
	Pro			590					595					600
	Ser			605					610					615
				620					625			_		630
	Leu			635					640					645
Lys	Ala	Lys	Pro	Lys 650	Val	Asn	Val	Lys	Pro 655	Ser	Val	Val	Lys	Val 660
Val	Ser	Ser	Pro	Lys 665	Leu	Ala	Pro	Lys	Arg 670	Lys	Ala	Val	Glu	Met 675
His	Ala	Ala	Val	Ile 680	Ala	Ala	Val	Lys	Pro 685	Leu	Ser	Ser	Ser	Ser 690
Val	Leu	Gln	Glu	Pro 695	Pro	Ala	Lys	Lys	Ala 700	Ala	Val	Ala	Val	Val 705
Pro	Leu	Val	Ser	Glu 710	Asp	Lys	Ser	Val		Val	Pro	Glu	Ala	
Asn	Pro	Arg	Asp		Leu	Val	Leu	Pro		Thr	Gln	Ser	Ser	
Asp	Ser	Ser	Pro		Glu	Val	Ser	Gly		Ser	Ser	Ser	Gln	
Ser	Met	Lys	Thr		Arg	Leu	Ser	Ser		Ser	Thr	Gly	Lys	
Pro	Leu	Ser	Val	Glu	Asp	Asp	Phe	Glu	Lys	Leu	Ile	Trp	Glu	Ile
Ser	Gly	Gly	Lys		Glu	Ala	Glu	Ile		Leu	Asp	Pro	Gly	
Asp	Glu	Asp	Asp	785 Leu 800	Leu	Leu	Glu	Leu	790 Ser 805	Glu	Met	Ile	Asp	795 Ser 810
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Arg Tyr Gly Met Pro Ile Asp Met Trp Ser Leu Gly Cys Ile Leu

				350	)				355	:				2.55
Ala	Glu	Leu	Leu	Thr	Gly	Tyr	Pro	Leu	Leu	Pro	. Gla			360 Glu
				365	•				370					2
Gly	Asp	Gln	Leu	Ala	Cys	Met	Ile	Glu	Leu	Len	Glv	Mat	Dro	375 Ser
				380	1				385					200
Gln	Lys	Leu	Leu	Asp	Ala	Ser	Lys	Arq	Ala	Lvs	Asn	Phe	Val	So~
				395					400					400
Ser	Lys	Gly	Tyr	Pro	Arg	Tyr	Cys	Thr	Val	Thr	Thr	Leu	Ser	ASD
				410					415					400
GLY	Ser	Val	Val	Leu	Asn	Gly	Gly	Arg	Ser	Arg	Arg	Gly	Lys	Leu
				442					4 3 N					42-
Arg	GIY	Pro	Pro	Glu	Ser	Arg	Glu	Trp	Gly	Asn	Ala	Leu	Lys	Gly
				440					445					450
Cys	Asp	Asp	Pro	Leu	Phe	Leu	Asp	Phe	Leu	Lys	Gln	Cys	Leu	Glu
Trn	λεπ	Dro	77.	455			_		460					465
115	Asp	Pro	Ата	470	Arg	Met	Thr	Pro	Gly	Gln	Ala	Leu	Arg	His
Pro	Tro	Len	λνα		7	<b>T</b>	_	_	475					480
		Leu	Arg	485	Arg	Leu	Pro	Lys		Pro	Thr	Gly	Glu	Lys
Thr	Ser	Val	Lvs		Tlo	Th~	C1	0	490					495
		Val	_, 5	500	116	1111	GIU	ser	Thr	Gly	Ala	Ile	Thr	Ser
Ile	Ser	Lys	Leu		Pro	Pro	go~	Com	505		_	_		510
				515		110	SEL	ser	520	Ala	Ser	Lys	Leu	
Thr	Asn	Leu	Ala		Met	Thr	Agn	ב ו ג	220	C1	<b>X</b>	~ n .		525
				530			пор	лта	535	GIY	ASI	тте	GIn	
Arg	Thr	Val	Leu	Pro	Lys	Leu	Val	Ser	ددد					540
				545	•			~~.						

<210> 14

<211> 416

<212> PRT

<213> Homo sapiens

<220>

<221> misc\_feature

<223> Incyte Clone Number: 1490070

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Lys Ala Met Glu Ser Lys Lys Thr Tyr Glu Gln Lys Cys Arg Asp 140 145 150 Ala Asp Asp Ala Glu Gln Ala Phe Glu Arg Ile Ser Ala Asn Gly 155 160 165
Ala Asp Asp Ala Glu Gln Ala Phe Glu Arg Ile Ser Ala Asn Gly
155 160 165
His Gln Lys Gln Val Glu Lys Ser Gln Asn Lys Ala Arg Gln Cys
170 175 180
Lys Asp Ser Ala Thr Glu Ala Glu Arg Val Tyr Arg Gln Ser Ile
185 190 195
Ala Gln Leu Glu Lys Val Arg Ala Glu Trp Glu Gln Glu His Arg
The The Cyc Clu No Dhe Cle Leu Cle Clu Dhe New York
Thr Thr Cys Glu Ala Phe Gln Leu Gln Glu Phe Asp Arg Leu Thr 215 220 225
215 220 225  Ile Leu Arg Asn Ala Leu Trp Val His Ser Asn Gln Leu Ser Met
230 235 240
Gln Cys Val Lys Asp Asp Glu Leu Tyr Glu Glu Val Arg Leu Thr
245 250 255
Leu Glu Gly Cys Ser Ile Asp Ala Asp Ile Asp Ser Phe Ile Gln
260 265 270
Ala Lys Ser Thr Gly Thr Glu Pro Pro Ala Pro Val Pro Tyr Gln
275 280 285
Asn Tyr Tyr Asp Arg Glu Val Thr Pro Leu Thr Ser Ser Pro Gly
290 295 300
Ile Gln Pro Ser Cys Gly Met Ile Lys Arg Phe Ser Gly Leu Leu
305 310 315
His Gly Ser Pro Lys Thr Thr Ser Leu Ala Ala Ser Ala Ala Ser
320 325 330
Thr Glu Thr Leu Thr Pro Thr Pro Glu Arg Asn Glu Gly Val Tyr
335 340 345
Thr Ala Ile Ala Val Glu Glu Ile Glu Gly Asn Pro Ala Ser Pro
350 355 360 Ala Gln Glu Tyr Arg Ala Leu Tyr Asp Tyr Thr Ala Gln Asn Pro
365 370 375
Asp Glu Leu Asp Leu Ser Ala Gly Asp Ile Leu Glu Val Ile Leu
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Glu Gly Glu Asp Gly Trp Trp Thr Val Glu Arg Asn Gly Gln Arg
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Gly Phe Val Pro Gly Ser Tyr Leu Glu Lys Leu
410 415
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Val	Leu	Val	Glu	Ala 50	Thr	Val	Lys	Leu	Asp 55	Glu	Leu	Val	Lys	Lys 60
Ile	Gly	Lys	Ala		Glu	Asp	Ser	Lys	Pro 70	Tyr	Trp	Glu	Ala	
Arg	Val	Ala	Arg	Gln 80	Ala	Gln	Leu	Glu	Ala 85	Gln	Lys	Ala	Thr	Gln 90
Asp	Phe	Gln	Arg	Ala 95	Thr	Glu	Val	Leu	Arg 100	Ala	Ala	Lys	Glu	Thr 105
Ile	Ser	Leu	Ala	Glu 110	Gln	Arg	Leu	Leu	Glu 115	Asp	Asp	Lys	Arg	Gln 120
Phe	Asp	Ser	Ala	Trp 125	Gln	Glu	Met	Leu	Asn 130	His	Ala	Thr	Gln	Arg 135
Val	Met	Glu	Ala	Glu 140	Gln	Thr	Lys	Thr	Arg 145	Ser	Glu	Leu	Val	His 150
Lys	Glu	Thr	Ala	Ala 155	Arg	Tyr	Asn	Ala	Ala 160	Met	Gly	Arg	Met	Arg 165
	Leu			170					175		_			180
-	Phe			185		-	-	-	190					195
_	Lys			200					205					210
	Glu	_	-	215			_		220					225
	Ile			230	_	_			235		-		_	240
	Gly		_	245					250					255
	Gly			260			_		265					270
	Phe		-	275		-			280				_	285
	Glu			290					295					300
	Ser			305	_				310			•		315
	Leu	_		320					325				_	330
	Phe			335	_		_		340	-		_		345
	Pro			350					355					360
	Asn			365					370					375
	Ser			380					385					390
	Pro			395					400					405
	Gln			410	GIÀ	Arg	Asp	GTA	11e 415	тте	Ala	Asp	шe	Lys 420
met	Val	GIn	шe	Gly 425										

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Ser Ser Leu Arg Asp Pro Ala Gly Ile Phe Glu Leu Val Glu Val
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Val Gly Asn Gly Thr Tyr Gly Gln Val Tyr Lys Gly Arg His Val
Lys Thr Gly Gln Leu Ala Ala Ile Lys Val Met Asp Val Thr Glu
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Asp Glu Glu Glu Ile Lys Leu Glu Ile Asn Met Leu Lys Lys 65 Tyr Ser His His Arg Asn Ile Ala Thr Tyr Tyr Gly Ala Phe Ile Lys Lys Ser Pro Pro Gly His Asp Asp Gln Leu Trp Leu Val Met 95 100 Glu Phe Cys Gly Ala Gly Ser Ile Thr Asp Leu Val Lys Asn Thr 110 115 Lys Gly Asn Thr Leu Lys Glu Asp Trp Ile Ala Tyr Ile Ser Arg 125 130 Glu Ile Leu Arg Gly Leu Ala His Leu His Ile His His Val Ile 145 His Arg Asp Ile Lys Gly Gln Asn Val Leu Leu Thr Glu Asn Ala 160 Gly Val Lys Leu Val Asp Phe Gly Val Ser Ala Gln Leu Asp Arg Thr Val Gly Arg Arg Asn Thr Phe Ile Gly Thr Pro Tyr Trp Met 190 Ala Pro Glu Val Ile Ala Cys Asp Glu Asn Pro Asp Ala Thr Tyr Asp Tyr Arg Ser Asp Leu Trp Ser Cys Gly Ile Thr Ala Ile Glu 220 Met Ala Glu Gly Ala Pro Pro Leu Cys Asp Met His Pro Met Arg 230 235 Ala Leu Phe Leu Ile Pro Arg Asn Pro Pro Pro Arg Leu Lys Ser 245 250 Lys Lys Trp Ser Lys Lys Phe Phe Ser Phe Ile Glu Gly Cys Leu 260 265 Val Lys Asn Tyr Met Gln Arg Pro Ser Thr Glu Gln Leu Leu Lys 275 280 His Pro Phe Ile Arg Asp Gln Pro Asn Glu Arg Gln Val Arg Ile 290 295 Gln Leu Lys Asp His Ile Asp Arg Thr Arg Lys Lys Arg Gly Glu 305 310 Lys Asp Glu Thr Glu Tyr Glu Tyr Ser Gly Ser Glu Glu Glu Glu 320 325 Glu Glu Val Pro Glu Gln Glu Gly Glu Pro Ser Ser Ile Val Asn 335 340 Val Pro Gly Glu Ser Thr Leu Arg Arg Asp Phe Leu Arg Leu Gln

		_		350					355					360
GIn	Glu	Asn	Lys	Glu 365	Arg	Ser	Glu	Ala		Arg	Arg	Gln	Gln	
T 0	C1-	<b>a</b> 1	<b>~1</b>		<b>.</b>	*	<b>a</b> 1	<b>~</b> 3	370	~1	_			375
Leu	GIII	GIU	GIN	Gln	Leu	Arg	GIU	GIn		Glu	Tyr	Lys	Arg	
T 011	T ON	- ר ת	C1	380	<i>a</i> 15	T >	λ	<b>7</b> 1.	385	<b>71</b> -	<b>03</b>	*	<b>a</b> 1	390
Беа	пец	Ala	GIU	Arg 395	GIII	ьуѕ	Arg	тте	400	GIII	GIN	ьуs	GIU	
Ara	λνα	λνα	Lau	Glu	G111	Cln	C12	7 ~~~		C1	N ====	C1	- ו מ	405
Arg	Arg	Arg	шеи	410	Giu	GIII	GIII	Arg	415	Gru	Arg	GIU	Ald	420
Arα	Gln	Gln	Glu	Arg	Glu	Gln	Ara	Δνα		Glu	Gln	Glu	Glu	
5		0211		425		0	9	9	430	OIU	GIII	010	014	435
Arq	Arq	Leu	Glu	Glu	Leu	Glu	Arg	Ara		Lvs	Glu	Glu	Glu	
	,			440			5	5	445	-1-				450
Arg	Arg	Arg	Ala	Glu	Glu	Glu	Lys	Arq		Val	Glu	Arq	Glu	
	_	_		455			•	_	460			_		465
Glu	Tyr	Ile	Arg	Arg	Gln	Leu	Glu	Glu	Glu	Gln	Arg	His	Leu	Glu
				470					475					480
Val	Leu	Gln	Gln	Gln	Leu	Leu	Gln	Glu	Gln	Ala	Met	Leu	Leu	His
				485					490					495
Asp	His	Arg	Arg	Pro	His	Pro	Gln	His	Ser	Gln	Gln	Pro	Pro	Pro
				500					505					510
Pro	Gln	Gln	Glu	Arg	Ser	Lys	Pro	Ser		His	Ala	Pro	Glu	
_			_	515	_				520					525
гàг	Ala	HIS	Tyr	Glu	Pro	Ala	Asp	Arg		Arg	Glu	Val	Pro	
A ====	Th.∽	Th~	Com	530	00=	Dwa	170 I	T	535	*	<b>3</b>	3	C	540
Arg	IIII	TILL	ser	Arg 545	ser	PIO	vai	Leu	550	Arg	Arg	ASP	ser	
T.011	Gln	Gly	Sar	Gly	Gln	Gln	Λcn	802		אן א	C111	GIn.	λνα	555
шец	GIII	Gry	SCI	560	GIII	GIII	Maii	Ser	565	Ата	GIY	GIII	Arg	570
Ser	Thr	Ser	Ile	Glu	Pro	Ara	Leu	Leu		Glu	Ara	Val	Glu	
				575		5			580		5			585
Leu	Val	Pro	Arq	Pro	Gly	Ser	Glv	Ser		Ser	Glv	Ser	Ser	
				590	-		•		595		_			600
Ser	Gly	Ser	Gln	Pro	Gly	Ser	His	Pro	Gly	Ser	Gln	Ser	Gly	Ser
				605					610					615
Gly	Glu	Arg	Phe	Arg	Val	Arg	Ser	Ser	Ser	Lys	Ser	Glu	Gly	Ser
				620					625					630
Pro	Ser	Gln	Arg	Leu	Glu	Asn	Ala	Val	Lys	Lys	Pro	Glu	Asp	Lys
_				635					640					645
Lys	Glu	Val	Phe	Arg	Pro	Leu	Lys	Pro		Asp	Leu	Thr	Ala	
n1-	<b>T</b>	<b>01</b>	T	650		** - 7	<b>61</b>	_	655	_	_	_		660
Ala	rÀs	GIU	ьeu	Arg	Ala	Val	Glu	Asp		Arg	Pro	Pro	His	
T = 17	ሞኮ≁	λαν	Тъ гъ	665 Ser	60*	Cor	Com	C1	670	Com	C1	mh.∽	Th.~	675
vai	1111	мър	ıyı	680	ser	ser	ser	GIU	685	ser	GIY	TILL	TILL	690
Glu	Glu	Asn	Δsn	Asp	Va l	Glu	Gln	Glu		Δ] =	Acn	Glu	Ser	
014	OLU	1105	1105	695	vai	OIU	OIII	Gru	700	ALG	лэр	OIU	DCI	705
Ser	Glv	Pro	Glu	Asp	Thr	Ara	Ala	Ala		Ser	Leu	Asn	Leu	
	1			710		9		••••	715	201	200			720
Asn	Gly	Glu	Thr	Glu	Ser	Val	Lvs	Thr		Ile	Val	His	Asp	
	•			725			4		730				- E-	735
Val	Glu	Ser	Glu	Pro	Ala	Met	Thr	Pro	Ser	Lys	Glu	Gly	Thr	
				740					745	_		_		750
Ile	Val	Arg	Gln	Thr	Gln	Ser	Ala	Ser	Ser	Thr	Leu	Gln	Lys	His
				<b>7</b> 55					760					765
Lys	Ser	Ser	Ser	Ser	Phe	Thr	Pro	Phe	Ile	Asp	Pro	Arg	Leu	Leu

				770					775					780
Gln	Ile	Ser	Pro	Ser	Ser	Gly	Thr	Thr	Val	Thr	Ser	Val	Val	Gly
				785					790					795
Phe	Ser	Cys	Asp	Gly	Met	Arg	Pro	Glu	Ala	Ile	Arg	${\tt Gln}$	Asp	Pro
				800					805					810
Thr	Arg	Lys	Gly	Ser	Val	Val	Asn	Val	Asn	Pro	Thr	Asn	Thr	Arg
				815					820					825
Pro	Gln	Ser	Asp	Thr	Pro	Glu	Ile	Arg	Lys	Tyr	Lys	Lys	Arg	Phe
				830					835					840
Asn	$\operatorname{\mathtt{Ser}}$	Glu	Ile		Cys	Ala	Ala	Leu	-	Gly	Val	Asn	Leu	
		_		845	_				850					855
Val	Gly	Thr	Glu		Gly	Leu	Met	Leu		Asp	Arg	Ser	Gly	
~-1	_		_	860	_		_	_	865	_			~->	870
GIY	Lys	Val	Tyr		Leu	TTE	Asn	Arg	_	Arg	Phe	Gin	GIn	
<b>3</b>	*** 1	T	<b>01</b>	875	T	3	77-7	T	880	m\	<b>+</b> 1 -	0	<b>03</b>	885
Asp	vaı	Leu	GIU	890	Leu	Asn	val	Leu		Thr	тте	ser	GIY	_
Tarc	7 cm	Lys	T OU		1721	Ф. гъ	Ф: г>-	T 011	895	There	τ ου	λ <b>~~</b> ~	7 an	900
Lys	Asp	цуs	ьeu	905	val	TYL	TYL	теп	910	irp	ьеи	Arg	ASII	915
Tle	I.em	His	Δen		Pro	Glu	Val	Glu		Lvc	Gln	Glv	מאש	
116	Бец	1113	ASII	920	110	GIU	vai	Giu	925	цуз	GIII	GIY	тър	930
Thr	Val	Gly	Asp		Glu	Glv	Cvs	Val		Tvr	Lvs	Val	Val	
		1		935		0-1	0,0		940	- 7 -	25,0			945
Tyr	Glu	Arg	Ile		Phe	Leu	Val	Ile		Leu	Lvs	Ser	Ser	
•		~		950					955		4			960
Glu	Val	Tyr	Ala	Trp	Ala	Pro	Lys	Pro	Tyr	His	Lys	Phe	Met	Ala
				965					970					975
Phe	Lys	Ser	Phe	Gly	$\operatorname{Glu}$	Leu	Val	His	Gly	Ser	Cys	Ala	Gly	Phe
				980					985					990
His	Ala	Val	Asp	Val	Asp	Ser	Gly	Ser	Val	Tyr	Asp	Ile	Tyr	Leu
				995					1000					1005
Pro	Thr	His	Ile	Gln	Cys	Ser	Ile	Lys	Pro	His	Ala	Ile	Ile	Ile
_				1010					1015	_				1020
Leu	Pro	Asn			Gly	Met	Glu			Val	Cys	Tyr		
~ 1	~-3			1025	_		_		1030			_		1035
Glu	GLY	Val			Asn	Thr	Tyr	_	_	Ile	Thr	Lys	_	
17	7	a1_		1040	<b>~</b> 1	W-+	D		1045	17- 7	77-	m		1050
vai	Leu	Gln	-	-	GIU	Met	PIO		Ser 1060	vai	Ala	Tyr		_
Sor	N can	C1-		1055	C111	TT 2-120	C1			27.	т1 о	<i>α</i> 3		1065
Ser	ASII	Gln		1070	GIY	пр	GTÅ		цуS 1075	Ala	116	Giu		1080
Ser	V=1	Glu			Иie	T.611	Δen			Dhe	Mat	Hic		
Ser	vaı	Giu		1085	1113	neu	Азр	-	1090	FIIE	Mec	птъ	-	1095
Ala	Gln	Arg			Phe	Len	Cvs			Asn	Asn	Lve		
	J_11	••••		1100	1110	<b></b> u	C 1 S		1105	11011	213 P	a, s		1110
Phe	Ala	Ser			Ser	Glv	Glv			Gln	Val	Tvr		
				1115		- <b>- 1</b>	1		1120			-1-		1125
Thr	Leu	Gly			Ser	Leu	Leu							
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<212> PRT

<213> Homo sapiens

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<220>
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<223> Incyte Clone Number: 1384286



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Leu	His	Asp	Ser	Ile 80	Ser	Glu	Glu	Gly	Phe 85	His	Tyr	Leu	Val	Phe 90
Asp	Leu	Val	Thr	Gly 95	Gly	Glu	Leu	Phe	Glu 100	Asp	Ile	Val	Ala	Arg 105
Glu	Tyr	Tyr	Ser	Glu 110	Ala	Asp	Ala	Ser	His 115	Cys	Ile	Gln	Gln	Ile 120
Leu	Glu	Ala	Val	Leu 125	His	Cys	His	Gln	Met 130	Gly	Val	Val	His	Arg 135
Asp	Leu	Lys	Pro	Glu 140	Asn	Leu	Leu	Leu	Ala 145	Ser	Lys	Cys	Lys	Gly 150
Ala	Ala	Val	Lys	Leu 155	Ala	Asp	Phe	Gly	Leu 160	Ala	Ile	Glu	Val	Gln 165
Gly	Asp	Gln	Gln	Ala 170	Trp	Phe	Gly	Phe	Ala 175	Gly	Thr	Pro	Gly	Tyr 180
Leu	Ser	Pro	Glu	Val 185	Leu	Arg	Lys	Glu	Ala 190	Tyr	Gly	Lys	Pro	Val 195
Asp	Ile	Trp	Ala	Cys 200	Gly	Val	Ile	Leu	Tyr 205	Ile	Leu	Leu	Val	
Tyr	Pro	Pro	Phe	Trp 215	Asp	Glu	Asp	Gln	His 220	Lys	Leu	Tyr	Gln	Gln 225
Ile	Lys	Ala	Gly	Ala 230	Tyr	Asp	Phe	Pro	Ser 235	Pro	Glu	Trp	Asp	Thr 240
Val	Thr	Pro	Glu	Ala 245	Lys	Asn	Leu	Ile	Asn 250	Gln	Met	Leu	Thr	Ile 255
Asn	Pro	Ala	Lys	Arg 260	Ile	Thr	Ala	His	Glu 265	Ala	Leu	Lys	His	Pro 270
Trp	Val	Cys	Gln	Arg 275	Ser	Thr	Val	Ala	Ser 280	Met	Met	His	Arg	Gln 285
Glu	Thr	Val	Glu	Cys 290	Leu	Lys	Lys	Phe	Asn 295	Ala	Arg	Arg	Lys	Leu 300
Lys	Gly	Ala	Ile	Leu 305	Thr	Thr	Met	Leu	Ala 310	Thr	Arg	Asn	Phe	Ser 315
Ala	Ala	Lys	Ser	Leu 320	Leu	Asn	Lys	Lys	Ala 325	Asp	Gly	Val	Lys	Pro 330
His	Thr	Asn	Ser	Thr 335	Lys	Asn	Ser	Ala	Ala 340	Ala	Thr	Ser	Pro	Lys 345
Gly	Thr	Leu	Pro	Pro 350	Ala	Ala	Leu	Glu	Ser 355	Ser	Asp	Ser	Ala	Asn 360
Thr	Thr	Ile	Glu	Asp 365	Glu	Asp	Ala	Lys	Ala 370	Arg	Lys	Gln	Glu	Ile 375
Ile	Lys	Thr	Thr	Glu 380	Gln	Leu	Ile	Glu	Ala 385	Val	Asn	Asn	Gly	Asp 390
Phe	Glu	Ala	Tyr	Ala 395	Lys	Ile	Cys	Asp	Pro 400	Gly	Leu	Thr	Ser	Phe 405
Glu	Pro	Glu	Ala	Leu 410	Gly	Asn	Leu	Val	Glu 415	Gly	Met	Asp	Phe	His 420
Arg	Phe	Tyr	Phe	Glu 425	Asn	Leu	Leu	Ala	Lys 430	Asn	Ser	Lys	Pro	Ile 435
			Ile	440					445			-		450
Ala	Ala	Cys	Ile	Ala 455	Tyr	Ile	Arg	Leu	Thr 460	Gln	Tyr	Ile	Asp	Gly 465
Gln	Gly	Arg	Pro	Arg	Thr	Ser	Gln	Ser	Glu	Glu	Thr	Arg	Val	Trp

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      His Arg Arg Arg
      Asp Gly Lys Trp Gln Asn Val His Phe His Cys Ser

      485
      485

      Gly Ala Pro Val Ala Pro Leu Gln

      500
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<210> 19 <211> 433 <212> PRT <213> Homo sapiens <220> <221> misc feature <223> Incyte Clone Number: 1512656 <400> 19 Met Thr Gly Glu Ala Gln Ala Gly Arg Lys Arg Ser Arg Ala Arg Pro Glu Gly Thr Glu Pro Val Arg Arg Glu Arg Thr Gln Pro Gly Leu Gly Pro Gly Arg Ala Arg Ala Met Ala Ala Glu Ala Thr Ala Val Ala Gly Ser Gly Ala Val Gly Gly Cys Leu Ala Lys Asp Gly 55 Leu Gln Gln Ser Lys Cys Pro Asp Thr Thr Pro Lys Arg Arg Arg 65 70 Ala Ser Ser Leu Ser Arg Asp Ala Glu Arg Arg Ala Tyr Gln Trp Cys Arg Glu Tyr Leu Gly Gly Ala Trp Arg Arg Val Gln Pro Glu 95 100 Glu Leu Arg Val Tyr Pro Val Ser Gly Gly Leu Ser Asn Leu Leu 110 115 Phe Arg Cys Ser Leu Pro Asp His Leu Pro Ser Val Gly Glu Glu 125 130 Pro Arg Glu Val Leu Leu Arg Leu Tyr Gly Ala Ile Leu Gln Gly 140 145 Val Asp Ser Leu Val Leu Glu Ser Val Met Phe Ala Ile Leu Ala 155 160 Glu Arg Ser Leu Gly Pro Gln Leu Tyr Gly Val Phe Pro Glu Gly 175 170 Arg Leu Glu Gln Tyr Ile Pro Ser Arg Pro Leu Lys Thr Gln Glu 185 190 Leu Arg Glu Pro Val Leu Ser Ala Ala Ile Ala Thr Lys Met Ala 200 205 Gln Phe His Gly Met Glu Met Pro Phe Thr Lys Glu Pro His Trp 220 Leu Phe Gly Thr Met Glu Arg Tyr Leu Lys Gln Ile Gln Asp Leu 235 Pro Pro Thr Gly Leu Pro Glu Met Asn Leu Leu Glu Met Tyr Ser Leu Lys Asp Glu Met Gly Asn Leu Arg Lys Leu Leu Glu Ser Thr 265 Pro Ser Pro Val Val Phe Cys His Asn Asp Ile Gln Glu Gly Asn

				225										
	_	_		275					280					285
Ile	Leu	Leu	Leu	Ser	Glu	Pro	Glu	Asn	Ala	Asp	Ser	Leu	Met	Leu
				290					295					300
Val	Asp	Phe	Glu	Tyr	Ser	Ser	Tyr	Asn	Tyr	Arg	Gly	Phe	Asp	Ile
				305					310					315
Gly	Asn	His	Phe	Cys	$\operatorname{Glu}$	Trp	Val	Tyr	Asp	Tyr	Thr	His	Glu	Glu
				320					325					330
Trp	Pro	Phe	Tyr	Lys	Ala	Arg	Pro	Thr	Asp	Tyr	Pro	Thr	Gln	Glu
				335					340					345
Gln	Gln	Leu	His	Phe	Ile	Arg	His	Tyr	Leu	Ala	Glu	Ala	Lys	Lys
				350					355					360
Gly	Glu	Thr	Leu	Ser	Gln	Glu	Glu	Gln	Arg	Lys	Leu	Glu	Glu	Asp
				365					370					375
Leu	Leu	Val	Glu	Val	Ser	Arg	Tyr	Ala	Leu	Ala	Ser	His	Phe	Phe
				380					385					390
Trp	Gly	Leu	Trp	Ser	Ile	Leu	Gln	Ala	Ser	Met	Ser	Thr	Ile	Glu
				395					400					405
Phe	Gly	Tyr	Leu	Asp	Tyr	Ala	Gln	Ser	Arg	Phe	Gln	Phe	Tyr	Phe
				410					415					420
Gln	Gln	Lys	Gly	Gln	Leu	Thr	Ser	Val	His	Ser	Ser	Ser		
				425					430					

<210> 20

<211> 527

<212> PRT

<213> Homo sapiens

<220>

<221> misc\_feature

<223> Incyte Clone Number: 2098635

<400> 20

Met Ser Leu Cys Gly Ala Arg Ala Asn Ala Lys Met Met Ala Ala Tyr Asn Gly Gly Thr Ser Ala Ala Ala Gly His His His His His His Leu Pro His Leu Pro Pro Pro His Leu Leu His His His Pro Gln His His Leu His Pro Gly Ser Ala Ala Ala 55 Val His Pro Val Gln Gln His Thr Ser Ser Ala Ala Ala Ala Ala 65 70 Ala Ala Ala Ala Ala Ala Ala Met Leu Asn Pro Gly Gln Gln 80 Gln Pro Tyr Phe Pro Ser Pro Ala Pro Gly Gln Ala Pro Gly Pro 95 100 Ala Ala Ala Pro Ala Gln Val Gln Ala Ala Ala Ala Thr 110 115 Val Lys Ala His His Gln His Ser His His Pro Gln Gln 125 130 Leu Asp Ile Glu Pro Asp Arg Pro Ile Gly Tyr Gly Ala Phe Gly 140 145 150 Val Val Trp Ser Val Thr Asp Pro Arg Asp Gly Lys Arg Val Ala 155 160 Leu Lys Lys Met Pro Asn Val Phe Gln Asn Leu Val Ser Cys Lys

				170					175					180
Arg	Val	Phe	Arg		Leu	Lys	Met	Leu		Phe	Phe	Lys	His	
Asn	Val	I.e.i	Ser	185 Ala	T.A11	Asp	Tle	Leu	190	Pro	Pro	Hic	Tle	195
ASII	Vul	neu	Ser	200	nea	лар	110	neu	205	FIO	FIO	1115	116	210
Tyr	Phe	Glu	Glu		Tyr	Val	Val	Thr		Leu	Met	Gln	Ser	
				215	-				220					225
Leu	His	Lys	Ile	Ile	Val	Ser	Pro	Gln	Pro	Leu	Ser	Ser	Asp	His
				230					235					240
Val	Lys	Val	Phe		Tyr	Gln	Ile	Leu	_	Gly	Leu	Lys	Tyr	
Wic	Sar	λla	Gly	245	Lau	His	7 ~~	λαν	250 Tle	Luc	Dro	Clar	) CD	255
1112	361	Ald	GLY	260	пец	1112	Arg	АБР	265	цуь	FIO	Gry	ASII	270
Leu	Val	Asn	Ser		Cvs	Val	Leu	Lvs		Cys	Asp	Phe	Glv	
				275	•			1	280	•	•		1	285
Ala	Arg	Val	${\tt Glu}$	Glu	Leu	Asp	${\tt Glu}$	Ser	Arg	His	Met	Thr	Gln	$\operatorname{Glu}$
				290					295					300
Val	Val	Thr	Gln	-	Tyr	Arg	Ala	Pro		Ile	Leu	Met	Gly	
7	TT-2 -	m	0	305		<b>T</b> 1.	<b>7</b>	T1 -	310	0	77- T	<b>a</b> 1	<b>G</b>	315
Arg	HIS	Tyr	ser	320	Ala	Ile	Asp	TTE	325	ser	vaı	GIY	Cys	330
Phe	Ala	Glu	Leu		Glv	Arg	Ara	Tle		Phe	Gln	Ala	Gln	
		014		335	O-1	5			340		0	1114	01	345
Pro	Ile	Gln	Gln	Leu	Asp	Leu	Ile	Thr	Asp	Leu	Leu	Gly	Thr	
				350					355					360
Ser	Leu	Glu	Ala		Arg	Thr	Ala	Cys		Gly	Ala	Lys	Ala	His
	_	_	~3	365	•	_	~ 7	_	370	_	_		_	375
тте	Leu	Arg	GIY	380	His	Lys	GIN	Pro	385	Leu	Pro	Val	ьeu	390
Thr	Leu	Ser	Ser		Ala	Thr	His	Glu		Va1	His	Len	Len	
	200			395				0.2.4	400	•42		LCu		405
Arg	Met	Leu	Val	Phe	Asp	Pro	Ser	Lys	Arg	Ile	Ser	Ala	Lys	Asp
				410					415					420
Ala	Leu	Ala	His		Tyr	Leu	Asp	Glu	_	Arg	Leu	Arg	Tyr	
	_		_	425	_	_	_,	_	430	_			_	435
Thr	Cys	Met	Cys	Lуs 440	Cys	Cys	Pne	ser	11nr	ser	Thr	GIY	Arg	Vai 450
Tvr	Thr	Ser	Asn		Glu	Pro	Val	Thr		Pro	Lvs	Phe	Asn	
-1-	****	001		455	014		• • • •		460	110	2,5	1110	110p	465
Thr	Phe	Glu	Lys		Leu	Ser	Ser	Val	Arg	Gln	Val	Lys	Glu	
				470					475			_		480
Ile	His	Gln	Phe	Ile	Leu	Glu	Gln	Gln	Lys	Gly	Asn	Arg	Val	
_				485	<b>.</b>	_			490	_	_			495
Leu	Cys	Ile	Asn		Gln	Ser	Ala	Ala		Lys	Ser	Phe	Ile	
Ser	Thr	Va I	פוע	500	Dro	Ser	Glu	Met	505 Pro	Pro	Ser	Pro	Len	510
JC1	****	vaı	VTQ.	515	110	UCL	OLU	1.100	520	110	DCI	110	neu	525
Trp	Glu													
_														

<210> 21

<211> 322

<212> PRT

<213> Homo sapiens

<220>

<221> misc\_feature <223> Incyte Clone Number: 2446646

<400> 21 Met Glu Gly Ile Ser Asn Phe Lys Thr Pro Ser Lys Leu Ser Glu Lys Lys Lys Ser Val Leu Cys Ser Thr Pro Thr Ile Asn Ile Pro Ala Ser Pro Phe Met Gln Lys Leu Gly Phe Gly Thr Gly Val Asn Val Tyr Leu Met Lys Arg Ser Pro Arg Gly Leu Ser His Ser Pro Trp Ala Val Lys Lys Ile Asn Pro Ile Cys Asn Asp His Tyr Arg Ser Val Tyr Gln Lys Arg Leu Met Asp Glu Ala Lys Ile Leu Lys 85 Ser Leu His His Pro Asn Ile Val Gly Tyr Arg Ala Phe Thr Glu 95 100 Ala Asn Asp Gly Ser Leu Cys Leu Ala Met Glu Tyr Gly Glu 110 115 Lys Ser Leu Asn Asp Leu Ile Glu Glu Arg Tyr Lys Ala Ser Gln 125 130 Asp Pro Phe Pro Ala Ala Ile Ile Leu Lys Val Ala Leu Asn Met 140 145 Ala Arg Gly Leu Lys Tyr Leu His Gln Glu Lys Lys Leu Leu His 155 160 Gly Asp Ile Lys Ser Ser Asn Val Val Ile Lys Gly Asp Phe Glu 170 175 Thr Ile Lys Ile Cys Asp Val Gly Val Ser Leu Pro Leu Asp Glu 185 Asn Met Thr Val Thr Asp Pro Glu Ala Cys Tyr Ile Gly Thr Glu Pro Trp Lys Pro Lys Glu Ala Val Glu Glu Asn Gly Val Ile Thr 215 Asp Lys Ala Asp Ile Phe Ala Phe Gly Leu Thr Leu Trp Glu Met Met Thr Leu Ser Ile Pro His Ile Asn Leu Ser Asn Asp Asp Asp Asp Glu Asp Lys Thr Phe Asp Glu Ser Asp Phe Asp Asp Glu Ala 260 265 Tyr Tyr Ala Ala Leu Gly Thr Arg Pro Pro Ile Asn Met Glu Glu 275 280 Leu Asp Glu Ser Tyr Gln Lys Val Ile Glu Leu Phe Ser Val Cys 295 Thr Asn Glu Asp Pro Lys Asp Arg Pro Ser Ala Ala His Ile Val 305 310 315 Glu Ala Leu Glu Thr Asp Val 320

<210> 22

<211> 802

<212> PRT

<213> Homo sapiens

<220>

<221> misc\_feature

<223> Incyte Clone Number: 2764911

<400> 22 Met Glu Glu Gly Gly Ser Ser Gly Gly Ala Ala Gly Thr Ser Ala Asp Gly Gly Asp Gly Glu Gln Leu Leu Thr Val Lys His Glu Leu Arg Thr Ala Asn Leu Thr Gly His Ala Glu Lys Val Gly Ile Glu Asn Phe Glu Leu Leu Lys Val Leu Gly Thr Gly Ala Tyr 50 55 Gly Lys Val Phe Leu Val Arg Lys Ile Ser Gly His Asp Thr Gly 65 70 Lys Leu Tyr Ala Met Lys Val Leu Lys Lys Ala Thr Ile Val Gln Lys Ala Lys Thr Thr Glu His Thr Arg Thr Glu Arg Gln Val Leu Glu His Ile Arg Gln Ser Pro Phe Leu Val Thr Leu His Tyr Ala Phe Gln Thr Glu Thr Lys Leu His Leu Ile Leu Asp Tyr Ile Asn Gly Gly Glu Leu Phe Thr His Leu Ser Gln Arg Glu Arg Phe Thr 140 145 Glu His Glu Val Gln Ile Tyr Val Gly Glu Ile Val Leu Ala Leu 155 160 Glu His Leu His Lys Leu Gly Ile Ile Tyr Arg Asp Ile Lys Leu 170 175 Glu Asn Ile Leu Leu Asp Ser Asn Gly His Val Val Leu Thr Asp 190 Phe Gly Leu Ser Lys Glu Phe Val Ala Asp Glu Thr Glu Arg Ala 200 205 Tyr Ser Phe Cys Gly Thr Ile Glu Tyr Met Ala Pro Asp Ile Val 215 220 Arg Gly Gly Asp Ser Gly His Asp Lys Ala Val Asp Trp Trp Ser 230 235 Leu Gly Val Leu Met Tyr Glu Leu Leu Thr Gly Ala Ser Pro Phe 245 250 Thr Val Asp Gly Glu Lys Asn Ser Gln Ala Glu Ile Ser Arg Arg 260 265 Ile Leu Lys Ser Glu Pro Pro Tyr Pro Gln Glu Met Ser Ala Leu 275 280 Ala Lys Asp Leu Ile Gln Arg Leu Leu Met Lys Asp Pro Lys Lys 290 295 Arg Leu Gly Cys Gly Pro Arg Asp Ala Asp Glu Ile Lys Glu His Leu Phe Phe Gln Lys Ile Asn Trp Asp Asp Leu Ala Ala Lys Lys Val Pro Ala Pro Phe Lys Pro Val Ile Arg Asp Glu Leu Asp Val 340 Ser Asn Phe Ala Glu Glu Phe Thr Glu Met Asp Pro Thr Tyr Ser Pro Ala Ala Leu Pro Gln Ser Ser Glu Lys Leu Phe Gln Gly Tyr 370 375 Ser Phe Val Ala Pro Ser Ile Leu Phe Lys Arg Asn Ala Ala Val 385 Ile Asp Pro Leu Gln Phe His Met Gly Val Glu Arg Pro Gly Val

				395					400					405
Thr	Asn	Val	Ala		Ser	Ala	Met	Met		Asp	Ser	Pro	Phe	
				410					415					420
Gln	His	Tyr	Asp	Leu 425	Asp	Leu	Lys	Asp	Lys 430	Pro	Leu	Gly	Glu	-
Ser	Dhe	Sar	Tla		Δνα	Lve	Cve	TeV.		Tare	Lare	Sar	Asn	435
DCI	1110	561	110	440	ALG	Lys	Cys	vai	445	Буб	цуз	SCI	ASII	450
Ala	Phe	Ala	Val		Ile	Ile	Ser	Lvs		Met	Glu	Ala	Asn	
	-			455				-4	460					465
Gln	Lys	Glu	Ile	Thr	Ala	Leu	Glu	Leu	Cys	Glu	Gly	His	Pro	
				470					475		_			480
Ile	Val	Lys	Leu	His	Glu	Val	Phe	His	Asp	Gln	Leu	His	Thr	Phe
				485					490					495
Leu	Val	Met	Glu		Leu	Asn	Gly	Gly		Leu	Phe	Glu	Arg	
_	_	_	_	500	-,	_	~ 3	em1	505		_	_	3	510
гàг	гуз	ràs	гàг		Pne	ser	GIU	Thr		Ala	Ser	Tyr	Ile	
7 ~~~	Y	T 011	17-1	515	<b>7</b> 7 7	T/ - 1	Com	II.	520 Mot	TT-2	7 ~~	ל הינו	Gly	525
Arg	пуъ	пец	vai	530	Ala	Val	DET	птэ	535	urs	Asp	vai	GTA	540
Val	His	Ara	Asp		Lvs	Pro	Glu	Asn		Len	Phe	Thr	Asp	
				545	-1-				550					555
Asn	Asp	Asn	Leu	Glu	Ile	Lys	Ile	Ile	Asp	Phe	Gly	Phe	Ala	Arg
				560					565		_			570
Leu	Lys	Pro	Pro	Asp	Asn	Gln	Pro	Leu	Lys	Thr	Pro	Cys	Phe	Thr
				575		_			580					585
Leu	His	Tyr	Ala		Pro	Glu	Leu	Leu		Gln	Asn	Gly	Tyr	-
Glu	Cor	Care	7 ~~	590	m-r-n	Cor	T 033	C1	595	т1 о	T 011	T	mha	600 Mot
Giu	SEL	Cys	ASP	605	пр	Ser	пец	Gry	610	116	ьеи	TAT	Thr	Met 615
Leu	Ser	Glv	Gln		Pro	Phe	Gln	Ser		Asp	Ara	Ser	Leu	
		4		620					625	<u>F</u>	3			630
Cys	Thr	Ser	Ala		Glu	Ile	Met	Lys	Lys	Ile	Lys	Lys	Gly	Asp
				635					640					645
Phe	Ser	Phe	Glu	Gly	Glu	Ala	$\mathtt{Trp}$	Lys	Asn	Val	Ser	Gln	Glu	Ala
•				650	~3	_	_		655	_	_	_	_	660
гÀг	Asp	Leu	тте	665	GLA	ьeu	Leu	Thr	070	Asp	Pro	Asn	Lys	-
Len	Lve	Met	Ser		T.em	Ara	ጥህም	Δen		Ттп	T.e.11	Gln	Asp	675
	2,5		201	680	Leu	**** 9	- 7 -	71511	685	110	шси	OIM	мър	690
Ser	Gln	Leu	Ser	Ser	Asn	Pro	Leu	Met		Pro	Asp	Ile	Leu	
				695					700					705
Ser	Ser	Gly	Ala	Ala	Val	His	Thr	Cys	Val	Lys	Ala	Thr	Phe	His
				710					715					720
Ala	Phe	Asn	Lys	-	Lys	Arg	Glu	Gly	Phe	Cys	Leu	Gln	Asn	Val
_	_		_	725		_	_	_	730					735
Asp	Lys	Ala	Pro		Ala	Lys	Arg	Arg		Met	Lys	Lys	Thr	
ምክም	Ser	Thr	۱۰۱ ای	740	Ara	Ser	202	Se*	745 Ser	۲۱۰۰	Co~	C-~	His	750 Ser
T111	DCI	1111	Jiu	755	ALG	DET	DEL	DEI	760	GIU	PET	Ser	1172	765
Ser	Ser	Ser	His		His	Glv	Lvs	Thr		Pro	Thr	Lvs	Thr	
				770		- 2	1 -		775			1 -		780
Gln	Pro	Ser	Asn	Pro	Ala	Asp	Ser	Asn	Asn	Pro	Glu	Thr	Leu	Phe
				785					790					795
Gln	Phe	Ser	Asp		Val	Ala								
				800										

<211> 641 <212> PRT <213> Homo sapiens <220> <221> misc\_feature <223> Incyte Clone Number: 3013946 Met Ala Thr Thr Val Thr Cys Thr Arg Phe Thr Asp Glu Tyr Gln 10 Leu Tyr Glu Asp Ile Gly Lys Gly Ala Phe Ser Val Val Arg Arg 20 25 Cys Val Lys Leu Cys Thr Gly His Glu Tyr Ala Ala Lys Ile Ile Asn Thr Lys Lys Leu Ser Ala Arg Asp His Gln Lys Leu Glu Arg 55 Glu Ala Arg Ile Cys Arg Leu Leu Lys His Ser Asn Ile Val Arg 70 Leu His Asp Ser Ile Ser Glu Glu Gly Phe His Tyr Leu Val Phe Asp Leu Val Thr Gly Gly Glu Leu Phe Glu Asp Ile Val Ala Arg 100 Glu Tyr Tyr Ser Glu Ala Asp Ala Ser His Cys Ile Gln Gln Ile 115 110 Leu Glu Ala Val Leu His Cys His Gln Met Gly Val Val His Arg 125 130 Asp Leu Lys Pro Glu Asn Leu Leu Ala Ser Lys Cys Lys Gly 145 Ala Ala Val Lys Leu Ala Asp Phe Gly Leu Ala Ile Glu Val Gln 155 160 Gly Asp Gln Gln Ala Trp Phe Gly Phe Ala Gly Thr Pro Gly Tyr 170 175 Leu Ser Pro Glu Val Leu Arg Lys Glu Ala Tyr Gly Lys Pro Val 190 185 Asp Ile Trp Ala Cys Gly Val Ile Leu Tyr Ile Leu Leu Val Gly 200 205 Tyr Pro Pro Phe Trp Asp Glu Asp Gln His Lys Leu Tyr Gln Gln 215 220 Ile Lys Ala Gly Ala Tyr Asp Phe Pro Ser Pro Glu Trp Asp Thr 230 235 Val Thr Pro Glu Ala Lys Asn Leu Ile Asn Gln Met Leu Thr Ile 245 250 Asn Pro Ala Lys Arg Ile Thr Ala His Glu Ala Leu Lys His Pro 265 Trp Val Cys Gln Arg Ser Thr Val Ala Ser Met Met His Arg Gln 275 280 Glu Thr Val Glu Cys Leu Lys Lys Phe Asn Ala Arg Arg Lys Leu 290 295 Lys Gly Ala Ile Leu Thr Thr Met Leu Ala Thr Arg Asn Phe Ser Ala Lys Ser Leu Leu Asn Lys Lys Ala Asp Gly Val Lys Pro Gln 320 325 Thr Asn Ser Thr Lys Asn Ser Ala Ala Ala Thr Ser Pro Lys Gly 335 340

<210> 23

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Thr Leu Pro Pro Ala Ala Leu Glu Pro Gln Thr Thr Val Ile His
Asn Pro Val Asp Gly Ile Lys Glu Ser Ser Asp Ser Ala Asn Thr
Thr Ile Glu Asp Glu Asp Ala Lys Ala Pro Arg Val Pro Asp Ile
                                     385
Leu Ser Ser Val Arg Arg Gly Ser Gly Ala Pro Glu Ala Glu Gly
                395
                                     400
Pro Leu Pro Cys Pro Ser Pro Ala Pro Phe Gly Pro Leu Pro Ala
                410
                                    415
Pro Ser Pro Arg Ile Ser Asp Ile Leu Asn Ser Val Arg Arg Gly
                425
                                    430
Ser Gly Thr Pro Glu Ala Glu Gly Pro Leu Ser Ala Gly Pro Pro
                440
                                    445
                                                         450
Pro Cys Leu Ser Pro Ala Leu Leu Gly Pro Leu Ser Ser Pro Ser
                455
                                    460
Pro Arg Ile Ser Asp Ile Leu Asn Ser Val Arg Arg Gly Ser Gly
                470
                                     475
Thr Pro Glu Ala Lys Gly Pro Ser Pro Val Gly Pro Pro Pro Cys
                485
                                    490
Pro Ser Pro Thr Ile Pro Gly Pro Leu Pro Thr Pro Ser Arg Lys
                500
                                    505
Gln Glu Ile Ile Lys Thr Thr Glu Gln Leu Ile Glu Ala Val Asn
                515
                                    520
Asn Gly Asp Phe Glu Ala Tyr Ala Lys Ile Cys Asp Pro Gly Leu
                530
                                    535
Thr Ser Phe Glu Pro Glu Ala Leu Gly Asn Leu Val Glu Gly Met
Asp Phe His Arg Phe Tyr Phe Glu Asn Leu Leu Ala Lys Asn Ser
                                     565
Lys Pro Ile His Thr Thr Ile Leu Asn Pro His Val His Val Ile
                 575
Gly Glu Asp Ala Ala Cys Ile Ala Tyr Ile Arg Leu Thr Gln Tyr
Ile Asp Gly Gln Gly Arg Pro Arg Thr Ser Gln Ser Glu Glu Thr
                                     610
Arg Val Trp His Arg Arg Asp Gly Lys Trp Gln Asn Val His Phe
                620
                                     625
His Cys Ser Gly Ala Pro Val Ala Pro Leu Gln
                635
```

<210> 24

<211> 588

<212> PRT

<213> Homo sapiens

<220>

<221> misc feature

<223> Incyte Clone Number: 067967

<400> 24

Met Gly Gly Thr Ala Arg Gly Pro Gly Arg Lys Asp Ala Gly Pro 1 5 10 15

Pro Gly Ala Gly Leu Pro Pro Gln Gln Arg Arg Leu Gly Asp Gly 20 25 30

Val Tyr Asp Thr Phe Met Met Ile Asp Glu Thr Lys Cys Pro Pro

				35					40					45
Cys	Ser	Asn	Val	Leu 50	Cys	Asn	Pro	Ser	Glu 55	Pro	Pro	Ser	Pro	Arg 60
Arg	Leu	Asn	Met	Thr 65	Thr	Glu	Gln	Phe	Thr 70	Gly	Asp	His	Thr	Gln 75
His	Phe	Leu	Asp	Gly 80	Gly	Glu	Met	Lys	Val 85	Glu	Gln	Leu	Phe	Gln 90
Glu	Phe	Gly	Asn	Arg 95	Lys	Ser	Asn	Thr	Ile 100	Gln	Ser	Asp	Gly	Ile 105
Ser	Asp	Ser	Glu	Lys 110	Cys	Ser	Pro	Thr	Val 115	Ser	Gln	Gly	Lys	Ser 120
Ser	Asp	Cys	Leu	Asn 125	Thr	Val	Lys	Ser	Asn 130	Ser	Ser	Ser	Lys	Ala 135
Pro	Lys	Val	Val	Pro 140	Leu	Thr	Pro	Glu	Gln 145	Ala	Leu	Lys	Gln	Tyr 150
Lys	His	His	Leu	Thr 155	Ala	Tyr	Glu	Lys	Leu 160	Glu	Ile	Ile	Asn	Tyr 165
Pro	Glu	Ile	Tyr	Phe 170	Val	Gly	Pro	Asn	Ala 175	Lys	Lys	Arg	His	Gly 180
Val	Ile	Gly	Gly	Pro 185	Asn	Asn	Gly	Gly	Tyr 190	Asp	Asp	Ala	Asp	Gly 195
Ala	Tyr	Ile	His	Val 200	Pro	Arg	Asp	His	Leu 205	Ala	Tyr	Arg	Tyr	Glu 210
Val	Leu	Lys	Ile	Ile 215	Gly	Lys	Gly	Ser	Phe 220	Gly	Gln	Val	Ala	Arg 225
Val	Tyr	Asp	His	Lys 230	Leu	Arg	Gln	Tyr	Val 235	Ala	Leu	Lys	Met	Val 240
			_	245			_		250				Ile	255
Ile	Leu	Glu	His	Leu 260	Lys	Lys	Gln	Asp	Lys 265	Thr	Gly	Ser	Met	Asn 270
Val	Ile	His	Met	Leu 275	Glu	Ser	Phe	Thr	Phe 280	Arg	Asn	His	Val	Cys 285
Met	Ala	Phe	Glu	Leu 290	Leu	Ser	Ile	Asp	Leu 295	Tyr	Glu	Leu	Ile	Lys 300
				305					310			_	Lys	315
Ala	Gln	Ser	Ile	Leu 320	Gln	Ser	Leu	Asp	Ala 325	Leu	His	Lys	Asn	Lys 330
Ile	Ile	His	Cys	Asp 335	Leu	Lys	Pro	Glu	Asn 340	Ile	Leu	Leu	Lys	His 345
	_	_		350		_			355		_		Ser	360
				365					370				Phe	375
				380					385	_			Pro	390
Asp	Ile	Trp	Ser	Phe 395	Gly	Cys	Ile	Leu	Ala 400	Glu	Leu	Leu	Thr	Gly 405
Gln	Pro	Leu	Phe	Pro 410	Gly	Glu	Asp	Glu	Gly 415	Asp	Gln	Leu	Ala	Cys 420
				425	_				430				Glu	435
Ser	Lys	Arg	Ala	Lys 440	Tyr	Phe	Ile	Asn	Ser 445	Lys	Gly	Ile	Pro	Arg 450
Tyr	Cys	Ser	Val	Thr	Thr	Gln	Ala	Asp	Gly	Arg	Val	Val	Leu	Val

				455					460					465
Gly	Gly	Arg	Ser	Arg	Arg	Gly	Lys	Lys	Arg	Gly	Pro	Pro	Gly	Ser
				470					475					480
Lys	Asp	Trp	Gly	Thr	Ala	Leu	Lys	Gly	Cys	Asp	Asp	Tyr	Leu	Phe
				485					490					495
Ile	Glu	Phe	Leu	Lys	Arg	Cys	Leu	His	Trp	Asp	Pro	Ser	Ala	Arg
				500					505					510
Leu	Thr	Pro	Ala	Gln	Ala	Leu	Arg	His	Pro	Trp	Ile	Ser	Lys	Ser
				515					520					525
Val	Pro	Arg	Pro	Leu	Thr	Thr	Ile	Asp	Lys	Val	Ser	Gly	Lys	Arg
				530					535					540
Val	Val	Asn	Pro	Ala	Ser	Ala	Phe	Gln	Gly	Leu	Gly	Ser	Lys	Leu
				545					550					555
Pro	Pro	Val	Val	Gly	Ile	Ala	Asn	Lys	Leu	Lys	Ala	Asn	Leu	Met
				560					565					570
Ser	Glu	Thr	Asn	Gly	Ser	Ile	Pro	Leu	Cys	Ser	Val	Leu	Pro	Lys
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Leu	Ile	Ser												

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<211> 389

<212> PRT

<213> Homo sapiens

<220>

<221> misc feature

<223> Incyte Clone Number: 346275

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Ser Asp Phe Gly Leu Ser Lys Met Glu Gly Lys Gly Asp Val Met 200 205 Ser Thr Ala Cys Gly Thr Pro Gly Tyr Val Ala Pro Glu Val Leu 220 215 Ala Gln Lys Pro Tyr Ser Lys Ala Val Asp Cys Trp Ser Ile Gly 230 235 Val Ile Ala Tyr Ile Leu Leu Cys Gly Tyr Pro Pro Phe Tyr Asp 245 250 Glu Asn Asp Ser Lys Leu Phe Glu Gln Ile Leu Lys Ala Glu Tyr 265 Glu Phe Asp Ser Pro Tyr Trp Asp Asp Ile Ser Asp Ser Ala Lys 280 Asp Phe Ile Arg Asn Leu Met Glu Lys Asp Pro Asn Lys Arg Tyr 295 Thr Cys Glu Gln Ala Ala Arg His Pro Trp Ile Ala Gly Asp Thr 310 Ala Leu Asn Lys Asn Ile His Glu Ser Val Ser Ala Gln Ile Arg 320 325 Lys Asn Phe Ala Lys Ser Lys Trp Arg Gln Ala Phe Asn Ala Thr 335 340 Ala Val Val Arg His Met Arg Lys Leu His Leu Gly Ser Ser Leu 355 Asp Ser Ser Asn Ala Ser Val Ser Ser Ser Leu Ser Leu Ala Ser 365 370 Gln Lys Asp Cys Ala Tyr Val Ala Lys Pro Glu Ser Leu Ser 380 385

<210> 26

<211> 343

<212> PRT

<213> Homo sapiens

<220>

<221> misc\_feature

<223> Incyte Clone Number: 283746

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Cys Ser Phe Leu Asp Asp Leu Leu Glu Leu Arg Asp Glu Glu Leu
Ser Lys Glu Ser Gln Glu Thr Asn Trp Phe Ser Ala Pro Ser Ala
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Leu Arg Val Tyr Gly Gln Tyr Leu Asn Leu Asp Lys Asp His Asn
Gly Met Leu Ser Lys Glu Glu Leu Ser Arg Tyr Gly Thr Ala Thr
                                     190
Met Thr Asn Val Phe Leu Asp Arg Val Phe Gln Glu Cys Leu Thr
                                     205
Tyr Asp Gly Glu Met Asp Tyr Lys Thr Tyr Leu Asp Phe Val Leu
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                                    220
Ala Leu Glu Asn Arg Lys Glu Pro Ala Ala Leu Gln Tyr Ile Phe
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                                    235
Lys Leu Leu Asp Ile Glu Asn Lys Gly Tyr Leu Asn Val Phe Ser
                245
                                     250
Leu Asn Tyr Phe Phe Arg Ala Ile Gln Glu Leu Met Lys Ile His
                260
                                     265
Gly Gln Asp Pro Val Ser Phe Gln Asp Val Lys Asp Glu Ile Phe
                275
                                     280
Asp Met Val Lys Pro Lys Asp Pro Leu Lys Ile Ser Leu Gln Asp
                290
                                     295
Leu Ile Asn Ser Asn Gln Gly Asp Thr Val Thr Thr Ile Leu Ile
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Asp Leu Asn Gly Phe Trp Thr Tyr Glu Asn Arg Glu Ala Leu Val
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Ala Asn Asp Ser Glu Asn Ser Ala Asp Leu Asp Asp Thr
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<211> 184

<212> PRT

<213> Homo sapiens

<220>

<221> misc\_feature

<223> Incyte Clone Number: 2696537

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<211> 118
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<213> Homo sapiens

<220>
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 His Trp Leu Ser Asn Leu Glu Ser Thr His Trp Leu Glu His Ile
                                     100
 Lys Leu Ile Leu Ala Gly Ala Leu Arg Ile Ala Asp Lys Val Glu
                                     115
 Ser Gly Lys Thr Ser Val Val Val His Cys Ser Asp Gly Trp Asp
                                     130
 Arg Thr Ala Gln Leu Thr Ser Leu Ala Met Leu Met Leu Asp Gly
 Tyr Tyr Arg Thr Ile Arg Gly Phe Glu Val Leu Val Glu Lys Glu
                 155
                                     160
 Trp Leu Ser Phe Gly His Arg Phe Gln Leu Arg Val Gly His Gly
                 170
                                     175
Asp Lys Asn His Ala Asp Ala Asp Arg Ser Pro Val Phe Leu Gln
                                     190
Phe Ile Asp Cys Val Trp Gln Met Thr Arg Gln Phe Pro Thr Ala
                200
                                     205
Phe Glu Phe Asn Glu Tyr Phe Leu Ile Thr Ile Leu Asp His Leu
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                                     220
Tyr Ser Cys Leu Phe Gly Thr Phe Leu Cys Asn Ser Glu Gln Gln
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Arg Gly Lys Glu Asn Leu Pro Lys Arg Thr Val Ser Leu Trp Ser
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Tyr Ile Asn Ser Gln Leu Glu Asp Phe Thr Asn Pro Leu Tyr Gly
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Ser Tyr Ser Asn His Val Leu Tyr Pro Val Ala Ser Met Arg His
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                                    280
Leu Glu Leu Trp Val Gly Tyr Tyr Ile Arg Trp Asn Pro Arg Met
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Lys Pro Gln Glu Pro Ile His Asn Arg Tyr Lys Glu Leu Leu Ala
Lys Arg Ala Glu Leu Gln Lys Lys Val Glu Glu Leu Gln Arg Glu
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<212> PRT

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FILE	GIII	Arg	Giu	65	GIU	ASII	цуз	DC1	70	110		002	5	75
Glu	Tyr	Asn	Val	Tyr	Ser	Thr	Phe	Gln	Ser	His	Glu	Pro	Glu	
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Asp	Tyr	Leu	гÀг	Ser 95	Leu	GIU	тте	GIU	100	гуѕ	TTE	MSII	пуъ	105
Arg	Trp	Leu	Pro	Gln	Gln	Asn	Ala	Ala		Phe	Leu	Leu	Ser	Thr
				110	_	_	_		115	_	<b>63</b> .		7	120
Asn	Asp	Lys	Thr	Ile 125	Lys	Leu	Trp	Lys	11e	Ser	GIU	Arg	Asp	Lуs 135
Arq	Ala	Glu	Gly	Tyr	Asn	Leu	Lys	Asp		Asp	Gly	Arg	Leu	
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Asp	Pro	Phe	Arg	Ile	Thr	Ala	Leu	Arg		Pro	Ile	Leu	Lys	Pro 165
Met	Asp	Leu	Met.	155 Val	Glu	Ala	Ser	Pro	160 Arg	Arq	Ile	Phe	Ala	
	-			170					175					180
Ala	His	Thr	Tyr	His	Ile	Asn	Ser	Ile		Val	Asn	Ser	Asp	
C111	Ψhχ	Тага	T.011	185 Ser	Δla	Acn	Asn	Len	190 Ara	Tle	Asn	Leu	Trp	195 His
Giu	1111	- y -	Lcu	200	1114	p	ор	200	205		•			210
Leu	Glu	Ile	Thr	Asp	Arg	Ser	Phe	Asn		Val	Asp	Ile	Lys	
	2	W-5	<i>α</i> 1	215 Glu	T 011	mb~	C1.,	1701	220	Thr	בות	λla	Glu	225 Phe
Ala	ASI	Met	GIU	230	Leu	TIIL	GIU	vaı	235	1111	AIG	ALU	GIU	240
His	Pro	His	Gln	Cys	Asn	Val	Phe	Val	Tyr	Ser	Ser	Ser	Lys	
		_	_	245	_		•		250	71-	T 4	C	A cro	255
Thr	Ile	Arg	Leu	Cys 260	Asp	Met	Arg	ser	265	Ala	ьeu	Cys	Asp	270
His	Ser	Lys	Phe	Phe	Glu	Glu	Pro	Glu		Pro	Ser	Ser	Arg	Ser
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Phe	Phe	Ser	Glu	Ile 290	Ile	Ser	Ser	IIe	295	Asp	vai	ьуs	Pne	300
His	Ser	Gly	Arg	Tyr	Met	Met	Thr	Arg		Tyr	Leu	Ser	Val	
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Val	Trp	Asp	Leu	Asn		Glu	Ser	Arg			Glu	Thr	His	330
Val	His	Glu	Tvr	320 Leu		Ser	Lys	Leu	325 Cys		Leu	Tyr	Glu	Asn
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Asp	Cys	Ile	Phe			Phe	Glu	Cys			Asn	Gly	Ser	Asp 360
Ser	Δla	Tle	Met	350 Thr		Ser	Tvr	Asn	355 Asn		Phe	Arq	Met	Phe
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Asp	Arg	Asp	Thr			Asp	Val	Thr			Ala	Ser	Arg	Glu
°°-	Cox		Dro	380		Car	Len	Lare	385		TAVS	. Val	Cvs	390 Thr
aeI	Sel	. Lys	, P.T.C	395		SEL	Leu	Lys	400		,		-, -, -	405
Gly	Gly	Lys	Arg			Asp	Glu	Ile			Asp	Ser	Leu	Asp
Dh -			, T	410		บ: ~	ጥሎ~	- הוה	415		. Dro	. Val	Acr	420 Asn
Pue	ASI	гъХг	ъъλε	425		nis	1111	MIG	430		, r.r.	, va.		435
Val	. I1e	a Ala	a Val			Thr	Asn	Asr	Lei	а Туз	: Ile	Phe	e Gln	Asp

445

440

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Lys Ile Asn

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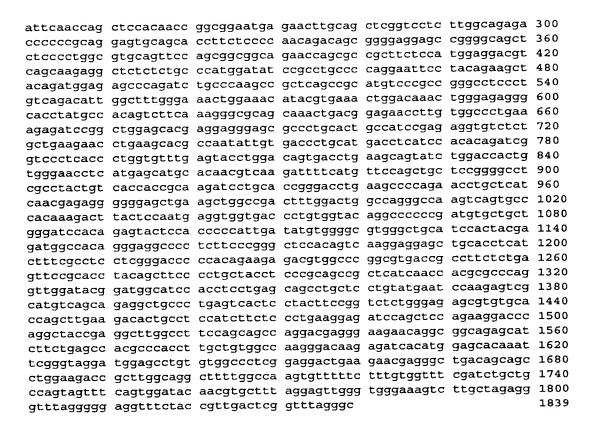
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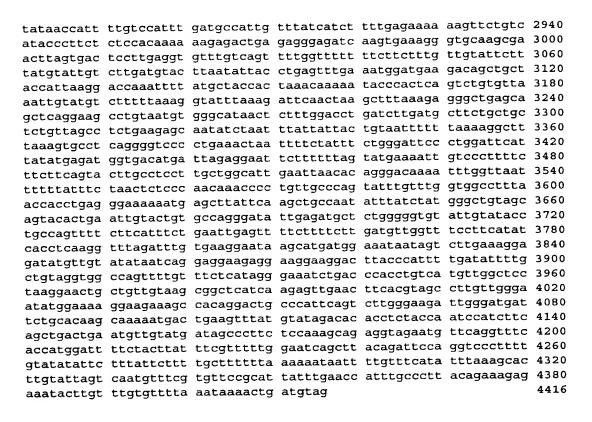
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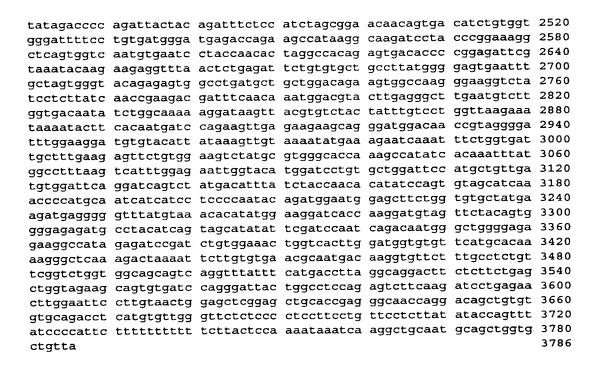
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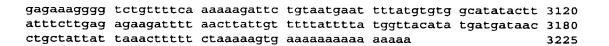
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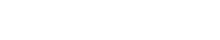
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#### SEQUENCE LISTING

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Gly Gly Asp Gly Leu Gly Gln Met Ser Leu Glu Phe Tyr Gln Lys 95 100 105

Lys Lys Ser Arg Trp Pro Phe Ser Asp Clu Cys 11s Pro Trp Glu 115 120

Val Trp Thr Val Lys Val Ris Val Val Ala Leu Ala Thr Glu Glm 125 130 138

Glu Arg Gln Ile Cys Arg Glu Lys Val Gly Glu Lys Leu Cys Glu 140 145 150

Lys Ile Ile Asn Ile Val Glu Val Met Asn Arg His Glu Tyr Leu 155 160 165

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Leu Ala Arg Ala Lys Ser Val Pro Thr Lys Thr Tyr Gor Asn Olu 290 295 Val Val Thr Leu Trp Tyr Arg Pro Pro Asp Val Leu Leu Gly Ser 305 310 Thr Glu Tyr Sor Thr Pro Ile Asp Met Trp Gly Val Gly Cys Ile 320 325 His Tyr Glu Met Ala Thr Gly Arg Pro Leu Pha Pro Gly Ser Thr 335 340 Val Lys Glu Glu Leu His Leu Ila Phe Arg Leu Leu Gly Thr Pro 350 Thr Glu Glu Thr Trp Pro Gly Val Thr Ala Phe Ser Glu Phe Arq 370 The Tyr Ber Phe Pro Cys Tyr Leu Pro Gin Pro Leu Ile Aen His 380 385 Ala Pro Arg Leu Asp Thr Asp Gly Ilc His Lou Lou Bor Bor Lou 395 400 Lou Lou Tyr Glu Ser Lye Ser Arg Met Ser Ala Glu Ala Ala Leu 410 415 Ser His Ser Tyr Phe Arg Ser Leu Gly Glu Arg Val His Gln Lou 425 43 D Glu Asp Thr Ala Ser lie Phe Ser Leu Lyz Glu Lie Gln Leu Gln 440 445 Lys Asp Pro Gly Tyr Arg Gly Leu Ala Pha Gln Gln Pro Gly Arg 455 46D Oly Lys Asn Arg Arg Gln Ser Ile Phe 470

<210> 6 <211> 540 <312> PRT <213> Home mapions <220>

<221> misc\_feature <223> Incyte Clone Number: 156108

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				400					7.70					135
1 -	•	<b></b>	Ora .	125	<b>-</b>		·		130	D.ST.	T 013	T • * C	mla si	
HIS	Agn	NEC	TUE	14D	PLO	790T	TIBIL	Hie	145	veh	nea	םענת	1111	150
f.an	r) a	Loui	Lan		A 09.	atu	Dha	Ric		fars	T) a	Ala	Aar	
WAII	116	nea.	пеп	155	#CII	Olu		1.46	160	-10		, , , , , , ,		165
/31 56	T.#11	ρ±τ.	Iva		Boot.	Mat:	Met	Eer	_	Sar	Gln	ser	Arq	
ur,		H-,	my :	170	5				175				_	180
Sec	Lve	Ber	Ala		Glu	Gly	Gly	Thr	Ile	:le	Tyr	Net	Pro	Pro
				185		-	_		190					195
Glu	Aen	Tyr	Glu	Pro	Oly	Gln	Lys	Ser	Arg	Ala	Ber	Ilo	Lyrs	His
				200					205					210
Asp	Ile	Tyr	Ser	Tyr	Ala	Val	lle	Thr	TTP	Glu	leV.	Leu	Ser	
				215			0		220				1	225
Lys	Gln	Pro	Ph≑		्रीस स	Val	Thr	Asn		Leu	Gin	IlB	net	
				230		<b>7</b>	T	rr. 1	235	3 414	лı	<i>7</i> 11	0-4	240 Leo
EBI	AST	ser	GIN		PIE	wr.ā	Pro	VAl	250	<b>₩.₽</b> 11	Gra	Q14	P-C-Y	255
Conta	m	3 444	T1 -	245	Ui n	i e e	hl =	Arg		Tle	Set	Len	Tle	
XIO	Tyt	нир	77.0	260	117.0	.π.≎	1777.74	T	265					270
Apr	Glv	TTO	Ala		Aen	Pro	Ago	Glu		Pro	9 <b>er</b>	Ph¢	ren	Lys
5.52	1			275			_		280					235
Cya	Leu	Ií≑	<b>Glu</b>	Lou	Glu	Pro	Val	Leu	Arg	Thr	Phe	Glu	Glu	elī
_				290					235					300
Thr	Phe	Leu	Glu	Ala	Val	Ile	Gln	Leu	Lys	Lys	Thr	Lyg	Leu	
				305					310					315
Ser	Val	9er	Ser		Ile	His	Leu	Сув		pàs	Lys	Lys	Met	330 GTB
	<u>.</u>		•	320	F	72-7	3 am	Ris	325	Dees	a1 s	alu	al n	
₽ <del>0</del> π	ber	Leu	ABO		PLO	AHI	чвп	13.1 15	340	FLU	GT:1	<b>61</b> tt		345
~	r]*•	Com	Car	335	T.#11	uie	Glu	Asn		Glv	Ser	Pro	Olu	
Clo	GIŞ	بليهان		350				. 16/16	355	~×			•	360
9er	Arg	Ser	Lou		Ala	Pro	Gln	Азр	Aen	Asp	Pha	Leu	Ser	Arg
				3€5					370					375
Lys	Ala	Gln	Авр	Сув	Tyr	₽he	Met	Lys	Leu	Sie	Hie	Cys	Pro	
				390					395					390
Aen	Rie	Ser	TŦÞ			Thr	Ile	Ber		Ser	Glo	W.â	Ala	
				395		-1			400		27.6	T7.0	тіа	405
Phe	Cya	Авр	H1e			THE	Pro	Cys	415	Ser	#T#	TTĒ	TTE	420
Due			. m	410		Z on	Bor	Glu		T. =11	Gla	Pro	Glv	
E.F.O	TICA	N-F	4 111	425		P. D.L.		-344	430				,	435
Ala	Glo	Gln	Tro			Ser	Lvs	Arc	Glu	App	Ila	Val	Asn	Gln
				440			•	-	445					450
Met	The	<b>Gl</b> u	Ala	Сув	Leu	Asn	: Gln	. Ser	Leu	Азр	Ala	Leu	Leu	8er
				455	i				450					465
Arg	Aaj	Leu	ılle	Met	Lye	Glu	yet.	Tyr			Val	8÷7	Thr	Lys
				470					475		_			400
Pro	This	Arg	Thr			Val	Arg	gla			. дар	ТЪІ	INI	A3p
	-1			489			T	. IT 7	490		(3.1 <b>–</b>	Tare	T.man	495 TAR
Ile	. GTI	ı Gly	, ATI	1 (91) 500		MT.	т пув	, AST	. 116		GTT.	- DAF	. 654	510
t or	1 A DT	n Tars	יום ב			r T.e.	ı Gle	) Pro			Glu	ı Ile	Let	val
entre E	. Ladi	ייניי	ינדנט כ	525					, .,. 520					525
Va]	Lees	e Are	y 9es			Le	а Аяс	a Leu			. Asr	Lys	Be:	: Met
		•		530					535					540

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Ala Lys Thr Asp Tie Asn Cys Gly Thr Asp Leu Net Pho Tyx Tie
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Glu Met Asp Pro Ero Ala Leu Pro Pro Lys Pro Pro Lys Fro Thr
Thr Val Ala Aen Aan Gly Met Asn Aen Aon Mot Ber Leu Gln Asp
                 50
                                      55
Ala Glu Trp Trr Trp Gly Asp Ile Ser Arg Glu Glu Val Aen Glu
                                      70
Lys Leu Arg Asp Thr Ala Asp Gly Thr Pha Lou Val Arg Asp Ala
                 60
                                      65
Ser Thr Lys Met His Gly Asp Tyr Thr Leu Thr Leu Arg Lye Gly
                  95
                                     100
Gly Asn Asn Lye Leu Ile Lye Ile Phe His Arg Asp Gly Lya Tyr
                110
                                     115
Gly Phe Ser App Pro Leu Thr Phe Ser Ser Val Val Glu Leu Ila
                125
                                     130
Asn His Tyr Arg Asn Glu Ser Leu Ala Gln Tyr Asn Fro Lys Leu
                140
                                     145
Asp Val Lyr Leu Lau Tyr Pro Val Ser Lys Tyr Gin Gin Asp Gin
                                     150
Val Val Lys Glu Asp Asn Ile Glu Als Val Gly Lys Lys Leu Eis
                 170
                                     175
Glu Tyr Asn Thr Oln Pho Gln Glu Lys Sor Arg Glu Tyr Asp Arg
                                     190
Leu Tyr Glu Glu Tyr Thr Arg Thr Ser Gln Glu Ile Gln Met Lye
                                     205
Arg Thr Ala Ile Glu Ala Phe Asn Glu Thr Ile Lys Ile Phe Glu
                                     220
Glu Gln Cys Gln Thr Gln Glu Arg Tyr Ser Lys Glu Tyr Ile Glu
                 230
                                     235
Lys Phe Lys Arg Glu Gly Agn Glu Lys Glu Ile Gln Arg Ile Met
                 245
                                     250
His Asn Tyr Asp Lys Leu Lys Ser Arg Ile Ser Glu Ile Ile Asp
                 26ú
                                     265
Ser Arg Arg Arg Leu Glu Glu Asp Leu Lys Lys Gln Ala Ala Glu
                 275
                                     280
Tyr Arg Glu Ile Asp Lys Arg Met Asn Ser Ile Lys Pro Asp Leu
                 290
                                     295
Ile Gln Lou Arg Lys Thr Arg Asp Gln Tyr Lou Met Trp Lou Thr
                 305
                                     310
Gln Lys Gly Val Arg Gln Lys Lys Leu Aan Glo Trp Leu Gly Asn
                 320
                                     325
Glu Asn Thr Glu Asp Gln Tyr Ber Leu Val Glu Asp Asp Glu Asp
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340

335

Leu Pro His His Asp Glu Lys Thr Trp Asn Val Gly Ser Ser Asn 255 Arg Asn Lys Ala Glu Asn Leo Leo Arg Oly Lys Arg Asp Gly Thr 370 265 Pha Leu Val Arg Glu Ser Sor Lys Gln Gly Cys Tyr Ala Cys Ser 305 380 Val Val Val App Cly Glu Val Lya Gis Cys Val Ile Asn Lys Thr 395 400 Ala Thr Gly Tyr Gly Phe Ala Glu Pro Tyr Asn Leo Tyr Ser Ser 415 410 Leu Lys Glu Lou Val Lou His Tyr Gln His Thr Ser Leo Val Gln 430 425 His Asn Asp Ser Leu Asn Val Thr Lou Ala Tyr Pro Val Tyr Ala Glo Glo Arg Arg

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215
                                     220
                                                         225
Lys Met Wro Asp Val Glu Leu Phe Val Asn Leu Gly Asp Trp Pro
                230
                                     235
Leu Glu Lys Lys Ser Asn Ser Azn Ile Hig Pro Ile Phe Ser
                245
                                     250
Trp Cys Gly Ser Thr Asp Ser Lys Asp Ile Val Met Pro Thr Tyr
                260
                                     265
                                                         270
Asp Lee Thr Asp Ser Vel Lee Glu Thr Met Gly Arg Val Ser Leu
                275
                                                         285
Asp Met Met Ser Val Glm Ala Asm Thr Gly Pro Pro Trp Glu Ser
                290
Lys Agn Ser Thr Ala Val Trp Arg Gly Arg Asp Ser Arg Lys Glu
                                     310
                                                         315
Arg Leu Glu Leu Val Lys Leu Ser Arg Lys His Pro Glu Leu Ile
                320
                                     325
Asp Ala Ala Phe Thr Asn Phe Phe Phe Lyz Hiz Asp Glu Asn
                335
                                     340
Leu Tyr Gly Pro Ile Val Lys Bis Ile Ser Phe Phe Asp Phe Phe
                350
                                     355
Lys Ris Lys Tyr Gln Rie Asn Ile Asp Gly Thr Val Ala Ala Tyr
                365
                                     370
                                                         375
Arg bed Pro Tyr Leu Leu Val Gly Asp Ser Val Val Leu Lys Gln
                360
                                     385
                                                         390
Amp Ser Ile Tyr Tyr Glu His Phe Tyr Aen Glu Leu Gln Pro Trp
                395
                                     400
                                                         405
Lys His Tyr Ile Pro Val Lys Ser Asn Lau Ser Asp Leu Leu Glu
                410
                                     415
                                                         420
Lys Leu Lys Trp Ala Lys Asp Siz Azp Glu Glu Ala Lys Lys Ile
                425
                                     430
                                                         435
Ala Lys Ala Gly Gln Glu Pho Ala Arg Asn Asn Lou Met Gly Asp
                440
                                     445
Asp Ile Phe Cys Tyr Tyr Phe Lys Leu Phe Gin Glu Tyr Ala Aen
                455
                                     460
Leu Gin Val Ser Glu Pro Glo Ils Arg Glu Gly Met Lys Arg Val
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                                     475
Glu Pro Gln Thr Glu Asp Asp Leu Phe Pro Cys Thr Cys His Arg
                485
                                     490
Lys Lys Thr Lys Asp Glu Leo
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Thr Pro Glu Ala Lys Asp Leu Ila Asn Lys Met Leu Thr Ila Asn 50· Pro Ala Lys Arg lls Thr Ala Ser Glo Ala Leu Lys His Pro Trp 70 65 Ile Cys Gln Arg Ser Thr Val Ala Ber Met Met His Arg Gln Glu 85 80 The Val App Cys Lou Lys Lys Phe Asn Ala Arg Arg Lys Leu Lys 100 95 Gly Ala Ile Leu Thr Thr Met Leu Ala Thr Arg Aso Pho Ser Ala 115 110 Ala Lys Ser Leu Leu Lys Lys Pro Asp Sly Val Lys Glu Ser Thr 130 125 Glu Ber Ber Asn Thr Thr Ile Glu Asp Glu Asp Val Lys Ala Arg 140 145 Lys Gln Glu Ile Ile Lys Val Thr Glu Glo Leu Ile Glu Ala Ile Asn Asn Gly Asp Phe Glu Ala Tyr Thr Lys Ils Cys Asp Pro Gly 175 170 Lou Thr Ala Phe Glo Pro Glu Ala Leu Gly Asn Leu Val Glu Gly 190 135 Met Asp Phe His Arg Phe Tyr Phe Glu Asn Ala Leu Ser Lys Ser 200 Asn Lys Pro Ile His Thr Ile Ila Lau Asn Pro His Val His Lau 220 215 Val Gly Asp Asp Ala Ala Cys Ile Ala Tyr Ile Arg Leu Thr Gin 330 235 Tyr Met Asp Gly Ser Gly Net Pro Lys Thr Met Gln Ser Glu Glu 250 245 Thr Arg Val Trp His Arg Arg Asp Gly Lys Trp Gln Asn Val His 265 360 Phe His Arg Ser Gly Ser Pro Thr Val Pro Ile Asn 275

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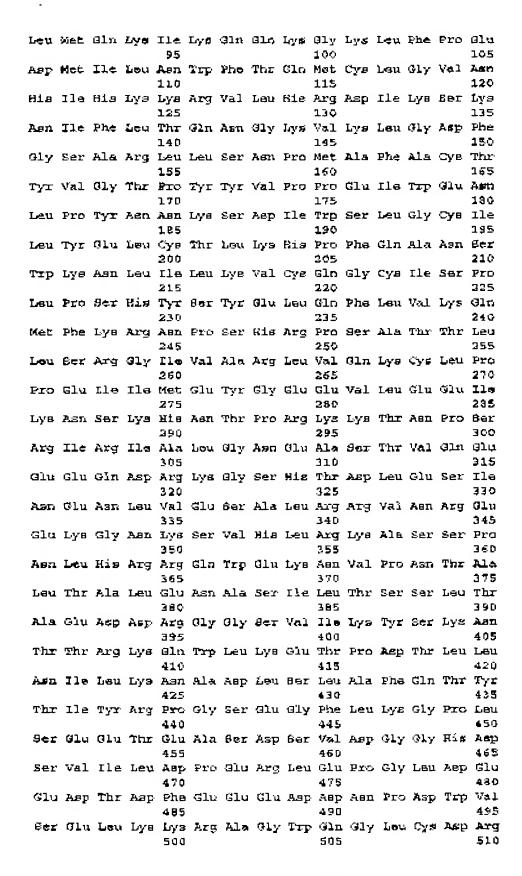
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 Met
 Lys
 Ala
 Asp
 Ile
 Lys
 Ile
 Trp
 Ile
 Leu
 Thr
 Gly
 Asp
 Lys
 Glu
 Ile
 Lys
 Lys</th



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The Pro Cys Pro Ser Ile Leu Glu Leu Glu Glu Leu Leu Arg Ala
Gly Lye Ser Ser Cye Ser Arg Val Asp Glu Val Trp Pro Asn Lou
The Ile Cly Asp Ala Met Asp Ser Leu Glo Lye Glo Asp Leu Arg
Arg Fro Lys Ile Ris Gly Ala Val Gln Ala Sor Pro Tyr Gln Pro
Pro Thr Leu Ala Ber Leu Gln Arg Leu Leu Trp Val Arg Gln Ala
Ala Thr Leu Asn His Ile Asp Glu Val Trp Pro Ser Lou Phe Leu
                 95
                                    100
Oly Asp Ala Tyr Ala Ala Arg Asp Lys Ser Lys Leu Ile Gln Leu
                                    115
                110
Gly Ile Thr His Val Val Azn Ala Ala Ala Gly Lys Pho Gln Val
                125
                                    130
Asp Thr Gly Ala Lys Pha Tyr Arg Gly Met Ber Leu Glu Tyr Tyr
                140
                                    145
Cly fle Glu Ala Asp Asp Asn Pro Phe Phe Asp Leu Ber Val Tyr
                155
                                    160
Phe Leu Pro Val Ale Arg Tyr Ile Arg Ala Ala Deu Ber Val Pro
                170
                                    175
Gln Gly Arg Val Leu Val His Cys Ala Ket Gly Val Ser Arg Ser
                185
                                    190
Ala Thr Leu Val Leu Ala Phe Leu Met Ilo Tyr Glu Asn Mot Thr
                200
                                     205
Low Val Glu Ala Ila Gln Thr Val Gln Ala His Arg Aen Ile Cys
                215
                                     220
Pro Asn Ser Cly Pho Leu Arg Cln Leu Cln Val Leu Asp Asn Arg
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Lau Gly Arg Glu Thr Gly Arg Phe
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Сув	The	Lys	Gly	Asp 20	Ser	Cye	Pro	Phe	Arg 25	Hís	Сув	Glu	Ala	Ala 30
		Asn		35					40					4,5
		Gln		50					55			_	-	50
		310		65					70				_	75
		Leu		90					95			•	_	90
		Leu		95					100					105
		Eer		110					115					120
		Asn		125					130					135
		Val		140					145					150
		Pro		155					160					165
		Asp		170					175			-		180
		Gln		185					190	_		_		195
		Arg		200					205				-	210
		Gly		215					220				-	225
		Lys		230					235			_		240
		Leu		245					<b>250</b>	_			_	255
		Arg		26D					265					270
		Glu		275					280			_		285
		Lya		290					295					300
		Leu		305					310					315
		Glu		320					325				•	330
		Asp		335					340					345
				350					355				•	360
		Glu		365					370					375
		Thr		360					365					390
		Ser Glu		395					400					405
STIME	OSI	GIH	AHT	TEM	WIH	GTIT	ኮልቴ	ι.Υ. <b>.</b> Ι	H7E	urg	AYU	OTU	ATI	wre

				410					415					42D
Glu	In reserve	cl n	Tara		Tager	Tavar	מינה מ			Ore	T1.	Tarë	Leu	
GLU	ьты	GIII	בענו	425	n) c	пус	мор	1111	430	~y~	***	<b>-</b> 17 6		435
Tak	lien	944	al n		ters	Tors	ጥኮታ	Wa 1		T.@11	Pro	ETO	115	
***	with	<b>~</b> ~~	O# !!	440	uya	My is	* ***	VOL	445	Deu	210	110		450
a l n	Car	Bra	alw		Car	She	Glu	Pro		(1) Ye	Lace	ጥከተ	Lys	
NI-3	Ser		217	455	<i>3</i>			110	460	4-1	<b>-</b> , -		<b>-</b> -, -	465
MAH	aln	(3) ss	We I	-	71 A	Team	ጥьታ	Lesis		en a	T] a	Lva	Leu	
2044	U			470		-, -	****	204	475			272		430
Lve	λla	t.an	Arm		Gln	Gln	EBT	Ser		ser	Ser	Thr	Ser	
272	,,			485					490					495
Pro	Ber	Gln	Him	-	Ala	Thr	Pro	Glv		Arq	Arg	Leu	Lau	Arq
				500				1	505	3				510
Ile	Thr	Lva	Arq		Gly	Ket	Lув	Glu	glų	Lys	Aan	Ļģd	Ģln	Glu
		•	_	515	-		-		520	•				525
Olv	Asn	Glu	Val	App	Ser	Gla	Яст	Øor	Ile	Arg	Thr	Glu	Ala	Lye
•				530					535					540
Glu	Ala	Ber	Gly	Glu	Thr	Thr	Gly	Val	Авр	lle	Thr	Lys	Ile	Gln
			-	545					550					555
Val	Lys	Arg	Cya	G1.v	ŢĿ	Met	Arg	Glu	Σуз	elH	Net	ĢГU	Ьув	<b>Gln</b>
				560					565					570
Gln	Glu	Arg	Glu	Lys	Ser	Val	Leu	Thr	Pro	Lеи	Arg	Gly	ysb	Val
				575					500					595
Ala	8er	CAA	Asn	The	Qln	Val	Ala	Glu	цуя	Pro	Val	Leu	Thr	
				590					595					600
Val	Pro	Gly	ïle		Arg	нів	Leu	Thr		Arg	Гец	Pro	Tite	
			_	505				_	610		<b>.</b> -		_	615
Ser	CEY	Gln	Lyn		Glu	Val	Glu	Thr		Gly	Ile	GIÄ	deA	
		_		620		-1-	- 1 -	a)-	625	Ŧ·		T	T	63D
Lau	Leu	APD	Val		Cys	Ala	ата	Gin		теп	ain.	гля	Arg	645
T			Time	635	**** 1	3.00	17 n 1	Taka	54Ü	0	72-7	57- T	Lys	
пун	итн	гуъ	FLO	650	431	VEII	Vall	пур	655	DCX	4.00	VAL	n j	660
32= 3	9	Ser	Bro.		T-211	à l a	book	Taze		TATE	Ala	val	Glu	
Y (4.4		PO#	-10	665	шоц	ALW			670	-,,,	****			675
Ria	Ala	Ala	Val		Ala	Ala	Val	Lve		Leu	Ser	Ber	Ser	
				690					605					690
Val	Leu	Gla	Glu		Pro	Ala	Lys	Ĺye		Ala	val	Ala	val	Val
				695				-	700					705
Pro	Leu	Val	Ser	alu	Asp	Lys	Ser	Val	Thr	Val	₽₽¢	Glu	als	Glu
				710	_	_			715					720
Asn	Pro	Arg	Авр	бer	Ŀви	Val	Lsu	Pro	Pro	Thr	gln	Ser	ser	Ber
				725					730					735
qeA	Ser	Ser	Pro	Pro	Glu	Val	Ser	gly	Pro	Ser	Şęr	Ser	Gln	Met
				740					745					750
Ser	Net	Lys	Thr	Arg	Arg	Ľsu	Ber	Ber	Ala	Ser	Thr	Gly	Lys	510
				755					760					765
PYO	Leu	Ser	Val		Aep	Asp	Phe	glu			Ila	Try	Glu	lle
				770					775					780
Ser	Gly	Gly	Lya			Ala	Glu	Ile			Укр	Pro	Gly	Гув
_		_		7 <b>8</b> 5				_	790				_	795
AKP	• <b>ଓ</b> 1ଅ	App	Aap	Leu	. Lieu	, L <b>¢</b> u	ցյա	Leu	Jer	Glu	Mat	Ile	деж .	Bet
				600					805					810

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Gly Gly Ser Lys His Thr Met Asn Asp His Leu His Val Gly Ser
His Ala His Cly Gin Ile Glo Val Arg Gin Leu Phe Glu Asp Asn
Ser Asn Lye Arg Thr Val Leu Thr Thr Gln Pro Asn Gly Lou Thr
                 50
                                     55
Thr Val Gly Lys Thr Gly Lou Pro Val Val Pro Glu Arg Gln Leu
                 65
Asp Ser lie Wis Arg Arg Gln Gly Ser Ser Thr Eer Leu Lys Ser
                 θÛ
                                      85
Met Glu Gly Met Gly Lys Val Lys Ala Thr Pro Met Thr Pro Glu
                                     100
Gln Ala Met Lys Gln Tyr Met Gln Lys Leu Thr Ala Fhe Glu His
                110
                                     115
His Glu Ile Phe Ser Tyr Pro Glu Ile Tyr Phe Leu Gly Leu Asn
                125
                                     130
Ala Lys Lys Arg Gln Gly Met Thr Gly Gly Pro Aso Aso Gly Gly
                140
                                     145
Tyr Asp Asp Asp Gln Gly Ser Tyr Val Gln Val Fro His Asp His
Val Ala Tyr Arg Tyr Glu Val Lou hys Val Ilc Gly Lys Gly Her
                 170
Phe Gly Gln Val Val Lys Ala Tyr Asp His Lys Val His Gln His
                                     190
Val Ala Leu Lys Met Val Arg Asn Glu Lys Arg Pho His Arg Glm
Ala Ala Glu Glu Ile Arg Ile Leu Glu His Leu Arg Lye Gln Asp
Lys Asp Asn Thr Met Asn Val Ils His Met Lou Glu Asn Phe Thr
                 230
                                     235
Phe Arg Asn His Ile Cys Met Thr Phe Glu Leu Leu Ser Met Asn
                 245
                                     250
Leu Tyr Glu Leu Ile Lye Lys Asn Lye Phe Gln Gly Phe Sex Leu
Pro Leu Val Arg Lys Phe Als His Ser Ile Leu Gln Cys Leu Asp
                 275
                                     290
Ala Leu His Lys Asn Arg Ile Ile His Cys Asp Leu Lys Ero Glu
                 290
                                     295
Asn Ile Leu Leu Lys Gin Gin Gly Arg Ser Gly Ile Lys Val Ile
                 305
                                     310
Amp Phe Gly Ser Ber Cys Tyr Glu Rim Gln Arg Val Tyr Thr Tyr
                 320
                                     325
Ile Gin Ser Arg Phe Tyr Arg Ala Pro Glu Val Ile Leu Gly Ala
                                     340
                 335
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Arg Tyr Gly Met Pro Ile Asp Mat Trp Ber Leu Gly Cys Ile Leu

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350
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                                                          350
Ala Glu Leu Leu Thr Gly Tyr Pro Leu Leu Pro Gly Glu Asp Glu
                 365
                                     370
                                                        375
Gly Asp Gln Lou Ala Cys Met Ile Glu Leu Leu Gly Met Pro Ser
                                     385
Gln Lys Lou Leu Asp Ala Ser Lys Arg Ala Lys Asn Pho Val Ser
                 395
                                     400
Ser Lys Gly Tyr Pro Arg Tyr Cys Thr Val Thr Thr Lau Ser Asp
                 410
                                     415
Gly Sar Val Val Leu Asn Gly Gly Arg Ser Arg Arg Gly Lys Leu
                 425
                                     430
Arg Gly Bro Pro Glu Ser Arg Glu Trp Gly Asn Ala Leu Lys Gly
                 440
                                     445
Cys Asp Asp Pro Lew Phe Lew Asp Phe Lew Lys Gin Cys Lew Glu
                455
                                     46D
Trp Asp Pro Ala Val Arg Met Thr Pro Gly Gla Ala Leu Arg His
                470
                                     475
Pro Trp Let Arg Arg Arg Let Pic Lys Pro Pro Thr Gly Glu Lys
                485
                                     490
Thr Ser Val Lys Arg Ile Thr Glu Ger Thr Gly Ale Ile Thr Ser
                                     505
The Ser Lys Lou Pro Pro Pro Ser Ser Ser Ala Ser Lys Leu Arg
                515
Thr Aen Lou Ala Gln Met Thr Asp Ala Aen Gly Aen Ile Gln Gln
                                     535
Arg Thr Val Leu Pro Lys Leu Val Ser
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<211> 416

<2125 PRT

<213> Romo sapiens

<220>

<221> misc feature

<223> Incyte Clone Number: 1490070

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125
Lys Ala Mot Glu Ser Lys Lys Thr Tyr Glu Gln Lys Cys Arg Rep
                140
                                     145
Ala Asp Asp Ala Glu Gin Ala Phe Glu Arg Ile Ser Ala Asm Gly
                155
                                     160
His Gin Lys Gin Val Glu Lys Bor Cin Asn Lys Ala Arg Gin Cys
                170
                                    175
Lys Asp Ser Ala Thr Glu Ala Glu Arg Val Tyr Arg Gln Ser Ile
                185
                                     190
Ala Gln Leu Glu Lys Val Arg Ala Glu Trp Glu Gln Glu His Arg
                200
                                     205
Thr Thr Cys Glu Ala Phe Gln Leu Gln Glu Phe Amp Arg Leu Thr
                215
Ile Lou Arg Asn Ala Leu Trp Val His Ber Aen Glo Leu Ser Met
Gin Cys Val Lys Asp Asp Glu Leu Tyr Glu Glo Val Arg Leu Thr
                                     250
Leu Glu Gly Cys Ser Ile Asp Ala Asp Ile Asp Ser Phe Ile Gln
                250
                                    365
Ala Lys Ser Thr Gly Thr Glu Pro Pro Ala Pro Val Pro Tyr Gln
                275
                                    280
                                                         265
Ash Tyr Tyr Asp Arg Glu Val Thr Pro Leu Thr Ser Ser Pro Gly
                290
                                    295
                                                         3 D D
Ile Gln Pro Ser Cys Gly Met Ile Lys Arg Pho Ser Gly Lou Leu
                305
                                    310
                                                         315
His Gly Ser Pro Lys Thr Thr Ser Leu Ala Ala Ber Ala Ala Ser
                320
                                    325
Thr Glu Thr Leu Thr Pro Thr Pro Glu Arg Asn Glu Gly Val Tyr
                335
                                     340
Thr Ala Ile Ala Val Glo Glu Ile Glo Gly Asn Pro Ala Ser Pro
                350
                                    355
Ala Glu Glu Tyr Arg Ala Leu Tyr Asp Tyr Thr Ala Gln Asn Pro
                365
                                    370
Amp Glu Leu Amp Leu Ser Ala Gly Amp Ils Leu Glu Val Ile Leu
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Glu Gly Glu Asp Gly Trp Trp Thr Val Glu Arg Asn Gly Gln Arg
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Gly Phe Val Pro Gly Ser Tyr Leu Glu Lys Leu
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<212> PRT

<213> Homo sapiene

<220×

<221> misc\_feature

<223> Incyte Clone Number: 1997814

<400× 15

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Gln Gly Glu Leu Glu Lys Leu Asn Gln Ser Thr Asp Asp 11e Asn
20 25 30
Arg Arg Glu Thr Glu Leu Glu Asp Ala Arg Gln Lys Phe Arg Ser

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Val	Leu	Val	Glu	Ala 50	Thx	Val	Lys	กอน	Asp SS	Glu	ኮ¢ለ	VSl	гуя	20 194
T1 e	01 v	INE	Ala		Glu	Aed	Ser	Lve		Tyr	Trp	Glu	Ala	Arg
	<b>V</b> -J	-,-		65				•	70	-	~			75
Arg	Val	Ala	Arg	Glo	Ala	Øln	Leu	Glu	Ala	glπ	Lys	ala	Thr	Gln
				80					85					30
<b>T</b> kb	Phe	<b>Gln</b>	Arg	Als	Thy	Glu	Val	Leu	Arg	Ala	Ala	Lys	<b>I</b> lu	Thr
				95					100					105
Ile	3er	Tea	Ala	Glu	${\tt Gln}$	УĽЭ	L¢પ	Leu		Yed	Asp	Lys	Arg	Gln
				110					115					120
Phe	увь	Ser	Ala		Gln	Glu	Ket	Ten		HIS	ALA	Thx	ĜΤĦ	Arg
				125			•	rm:	130		a1	Len	1r1	135
Val	Met	Glu	Ala		Gln	Thr	Lys	THE		Ser	GTI	Геп	Vall	150
		<b>m</b>	<b>.</b>	140	3	COn cas	3.00	2.10	145	Hat	Clin	Lycy	Mat	
Lyr≄	GIU	Thr	H1#		wig	Tyr	иеп	WIH	160	mer	GLY	Wâ	FUEL	165
m3 =	T 534	۳٦.,	Turn	155	Len	fara	) No.	Z1a		Len	LMS	9er	Lve	
GIII	ГВП	13 I U	гув	170	Par	My 3	V+A	A 44	175	24.4	~_ <b>, ~</b>		, -	100
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Iwa	Lva	Thr	Val		Ast	Çı¢ıl	Gln	Ale	Lye	Leu	Thr	Leu	Ala	Lys
-3-	-,-			200	-				205					210
Gly	Glu	Tyr	Lye	Met	Ala	Leu	ьуз	Aso	Leu	Glu	Met	Ile	9¢r	Apr
_				21,5					220					225
Glu	110	His	Glu	Arg	Arģ	Arg	Çer	Şer	BLA	Met	Gly	PYC	Аrg	Gly
				23 D					235		_			240
СУВ	Gly	Val	Gly	ala	Glu	Gly	Ser	ser		Ser	Val	Glu	ABD	
				245		_	_		250		25- 3			255
FTO	Gly	Sar	Lyp		Glu	Pro	App	ALA		Ret	VAL	elA	Ser	370
		-1	•	250				T	265	16-3	6	ക്കും	3 pm	
YIA	rne	GII	. Aep	авр 275	ser	cys	per	ABII	280		06.1	Glu	ver	235
04.4	atis	TVI v	- /31 -4		T/a 1	044	Ser	Phe			Glv	Pro	Thr	
aer	614		44,1	290	•				295		,			300
Pro	6ar	Glu	Met		ABD	Gla	Phe	Pro			Val	Arg	Pro	oly
	5-02			305					310					315
8er	Lev	Asp	Lev	PTO	Ber	Pro	Val	Ser	Leu	Ser	Glu	Phe	Gly	Met
				320					325					330
Ket	Phe	Pro	Val	. Leu	Gly	Pro	Arg	Ser	Glu	Сув	e e e	Gly	Ala	9er
				335					340		_	_		345
₽¢r	Pro	Glu	. Сув	Glu	Val	Ģlu	yxg	Giy			Ala	. Glu	GTÅ	Ala
				350				_	355					350
Glu	ABI	LLYE	Thi			Lye	Ala	Aen			1 WEG	i ATA	. nen	Ser 375
_				365					370		. 👌	. 2at	Ант	
Ser	, R <del>¢</del> ĭ	## <b>#</b>	נגט :			. сту	, ser	. SEI	385 385		. GII	I Dez	DO	Thr 390
سد ف	- D	٠	, (-1-	386 : Gle		. T.e.	, (3)	Z eor			LVA	Glr	ı Ler	Ser
DHI	FIL	י ישבו	* 621)	3 <b>9</b> 5		ייפוני			400		,-			405
Ţ,was-	1 (31 <del>-</del>	t Page	a Alman			Am	, Ast	gl:			. Ala	a Aet	) Ile	Lуэ
		. ~y*		410		• • • •	,r#E	1	41	5		•		420
Met	: Val	Gli	a Il	e Gly										
				429										

<210> 16 <211> 1135 WO 00/06728 PCT/US99/17132

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340

Glu Glu Val Pro Glu Glu Glu Gly Glu Fro Ser Ser Ile Val Asn

Val Pro Gly Glu Ser Thr Leu Arg Arg Asp Pha Leu Arg Leu Gla

335

				350					355					360
Gln	Glu	ABD	Lye		yrd	₽≑≭	Glu			Arg	Frd	GTU		
	_			365					370		<b></b>			375
Leu	Gln	Glu	Gln		Ľeu	W.à	Glu	Gin		Glц	<b>ት</b> አ	rĂŧ		
		_	_	380		_	_		365		-7-	•		390 
Lau	Leu	Ala	Glu		Gln	Lys	भरत			GII	GIR	тлв	RIG	
			_	395			-4-7		400	<b>~</b> • • • •	<b>3</b>	m3	27.5	405
Arg	yzű	Yrd	Leu		Glu	Glrı	GTD			GIU	arg	ATIT	WIR	420
_				410		-2	<b>3</b>		415	en	A1	A12.55	. <del></del>	
yrá	GIU	Gln	GIU		GIII	Gln	arg	WEÖ		GII	'2TIT	GLU	914	435
_		•	<b>773</b>	425	T	21 <b>1.</b>	*	T. 2-2	430	Term	cla	Glu	Glu	
Arg	Arg	ren	G1#		Den	Glu	P.I. y	wig	992 ETG	пуз	31.11	31.0	Gru	450
_	_	<b>-</b>	• 1 -	440	<b>~</b> 1	C3	T s.e.	7		₹7 <b>-</b> -1	e1.5	Ti se m	@lar	
AIG	Arg	hrg	WIH		GIU	Glu	रात्रीक	wra	450	AST	OT4	ша	GIU	465
	_		•	425	<b>-</b> 1-	T	23.0	est o		<b>63</b> H	Ti	G i er	T 11	
Ulu	Tyr	ILe	ATT		GIN	Leu	GIU	дтп	475	ĠŢ1]	wrâ	HTM	74 (t	460
1	_	-1-	-1-	470	7.00	T 414	231 A	A11		70 T -	Mot	Lou	T211	
VAL	Геп	GTD	GII		PEA	L≑u	ATH	ATI		wig	ner.	Tield	TI-GIT	495
				405	19.2 -	Pro	<u>مار</u>	wê o	490	C) n	σιи	Dro	Dro	
wab	HIE	AZG	भग्रम		27.3	RIC	ATT.	птн	505	GIII	ייים	FLU	110	51.0
	423	A17	ф1	500	0.00	Lya	Dvc.	Пач	-	ude.	31-	Pro	<b>41</b> 11	
PEO	GII	GIR	GIU	515	GAI	гуа	PIU	OCT	520	****	A-14	• • •		525
T	.1.	778	Ma		D	Ala	ħ nn	8	_	2 777	/2] n	val	Pro	
гÃЯ	WIH	HIB	134	530	FLO	~~~	uro f.	TT 9	535	***=3		•		540
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LT. A	1111	7111	Der	545	361	T.T.	101		550					555
Tarib	<b>01</b> 4	/33.44	0		മാം	Gln	пол	Sev		Ala	glv	Gin	Arg	
π∉ή	CT11	217	MAT	560	911	GIU.	112311		565		7			570
An-	ጥኮታ	Por	Tle		Pro	Arg	Len	11 <b>خر</b> آ	-	Glu	Arg	Val	Glu	
DAT	1111	пог	116	575	110	9			560					535
T.e.s	Val.	Pro	Aro		al <sub>v</sub>	Boz	αlν	ser		Ser	Gly	Ser	Ser	Aen
21,54	• • • •		9	590	1		2		595		-			600
a-y	alv	Ber	GD.n		Glv	Ber	Hia	Pro		9er	Ģln	ger	Gly	Ser
7.011				605					610					615
Glv	Glu	Ara	Phe	Arq	Val	Arg	Ser	Ser	Ser	Lув	Ber	Glu	Gly	Ber
				620		_			625	_				630
Ртр	Ber	Gln	Arq			Asn	Ala	Val	Lys	Lys	Pro	Glu	Авр	Lys
				<b>635</b>					640	-				645
Lys	013	Val	Ph⊜			Lou	Lya	Pro	Ala	Авр	Leu	Thr	Ala	Lau
-				650			_		655					660
Ala	Lys	Glu	Leu	Arg	Ala	val	Glu	Aug	Val	Axy	Pro	Pro	His	Lyp
	_			<b>665</b>	i				670					675
Val	Thr	Азр	Tyr	9 <b>¢</b> x	: #er	Ger	Ser	Glu	Glu	Set	Gly	Thi	Thr	узр
				€80					565					690
Ģλυ	G1.0	Aup	Авр	Аер	Yal	Glu	Gln	Glu	Gly	Als	. Aep	Glu	Ser	Thr
				695					700					705
Ser	Gly	Pro	alu	AEY	Th:	Arg	Ala	Ala			Let	ı Abi	រោមប្រ	Ber
				710					715					720
ABI	Gly	dlu.	Thr	Gli	ı Set	val	. Lye	. ጉካ <del>ታ</del>	Met	: Ile	Val	L Hid	) Asp	APP
				725					730					735
Val	L Gli	941	: Gla	r Fra	Ala	. Met	Thr	PTC			Gli	ı Gly	/ Thr	Leu
				740					745					750
Ϊlε	a Val	Arg	, Gli	ı Thi	r Olr	ı Ser	ولھ:	1 4 t			Lou	ı Əlt	r <b>ጉ</b> ላቁ	HTW
				75					760					765
Lye	g 945	e Ser	9¢,	: 9 <b>e</b> :	r Phe	The	Pro	> Phe	• Ile	e yel	p Pro	o Ari	1 rec	ren

e17	<b>+</b> 1 -			770		-1		1	775				,	780
ATD	116	Ber	Pro		вer	GLY	ZUL	THY		Thr	ser	ATT	Val	_
Tile o	C	~	D.o.s	785		3	<b>D</b>		790	77.	•	<i>4</i> 2 .		795
PINE	Ser	Сув	wab		wet	wid	Pro	(31)t		TYC	Arg	GTM	Дэр	
				600		,	_		605	_		_	_,	610
THE	wrg	гуа	GIY		vai	vai	Aan	Val		Pro	Thr	Aen	Thr	_
<b>D</b>			<b>.</b>	815	<b>-</b>		-1.		820		_	_	_	825
Fro	ATM	Her	wab		Pro	GTA	me	rig		lyr	гÀъ	ГÄВ	Arg	
	_	41		630				_	635			_	_	840
ABI	Ber	GLU	116		суэ	WT9	νтя	Lau	_	GIA	AST	ABN	Leu	
37.5		md	a3	845		•	••	•	850	•	•		~** · · ·	855
VAI	ату	Thr	GIU		GIĀ	гел	met	Τ÷Π		Aep	arg	Her	Gly	
A(2		- d- 1		660	<b>.</b>		3		865		P-1	45	<i>2</i> 47	970
Giy	гåа	vail	Tyr		Ten	TTG	Asn	wad	_	arg	ы	GIR	Gln	
	**. 3	7		975 21	• • • •	•		•	880		<b>+-</b> .	<b>a.</b> .		885
ADD	AsT	Leu	GTÜ		Tén	ABn	VBI	1-511		Tur	TTE	Ret	gly	•
T	T	F	<b>T</b>	890	T	<b></b>	<b>-</b>		695		<b>-</b>		<b>-</b>	<b>∌</b> 00
гλя	web	Був	rea	_	AST	Tyr	тут	D-S11		Trp	T49II	vid	Aen	_
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116	PQ/I	HID	ABR	920	1.Lú	ήŤЙ	€ D.T.	u	_	nya	Will	GTÅ	J.тр	
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Inr	ATT	GLY	veb		210	GIA	Сув	ART		Tyr	r.N.a	ABI	Val	_
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alm	\$5 <b>-</b> 1	The second	<b>3.7</b> -		81-	D	Lavo	Been		ui a	farm	tibo	Mec	960 81-
324	VAL	131	N.T.	965	wid	FLO	пля	RIU	97D	игн	пЪв	E.∏44	Nac	975
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	Dyo		111	980	914	nea	441	1111	985	GCL	-70	nia	217	390
Him	Ala	Val	3 000		3 cm	Ser	GT tr	Ser		The same	Lan	T) æ	Туг	
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Pro	Thr	нів	Ile		CVB	Ber	Tle			Hia	ALS	Tla	Ile	
				1010	-,-			_	1015					1020
. Leu	Pro	Agn			Gly	Net	glu			Val	Cva	Tvr		
				1025	•				1030	•••		•		LOSS
Glu	Gly	Val			asa	Thr	Tyr			Ile	Thr	Lys	Aep	
	•		_	1040				_	1D45			_,_	_	L050
Val	Len	Glu	Tro	Gly	Glu	Met	Pro	Thr	Ser	Val	Ala	Tyr	I1∉	
				1055					1060			•		L065
Ber	Aan	Gln	Thr	Ket	Gly	Tim	Ğly	Glu	Lye	Ala	Ile	Glu	Ile	Arg
				1070	•	•	•		1075					LOBO
Ser	Val	Glu	Thr	Gly	Him	Leu	App	Gly	Val	Pho	Not	Rid	Lys	Ara
				1005				_	1090					1095
Ala	Gln	Arg				Leu	Сув				Azp	Lye	Val	
		_		1100			-		1105		-	-		1110
Phe	Ala	Bor			9ez	Gly	Gly			Oln	Val	Tyr	Pho	
				1115		•	-		1120			•		1125
Thr	Leu	Gly	Arg	Thr	Ser	Leu	Leu	Ser	Trp					
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<213> Homo sapiens

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<220>
<221> misc\_feature

<323> Incyte Clone Number: 1384286

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Glu	Ala	Arg	Ila		Arg	Leu	Leu	Lys		Ser	Asa	Il-	Val	
T -244	Tid a	Bene	0.44	65 Tab	n	<i>~</i>	<b>a</b> 3	43	70		_	_	v. 3	75
Tvi i	HIB	yep	AÇI	80	acr	ЭTЙ	ATT	OTA	1/1/8 85	HIP	туг	Leu	var	Phe 90
Aap	Leu	val	Thr		Gly	Glu	Leu	Phe		Asp	Ţlę	Val	Ala	
				95					100	_				105
<b>Gl</b> u	TXT	Tyr	Ser		Ala	Азр	Ala	ßer		Сув	$_{\mathbf{Ile}}$	Gln	Gln	
Loses	Glu	Ala	11-7	110	นสถ	-Ciro	Trick on	alu.	115	G1	5T6 1		174 -	120
nea	GIU	NT.	AGTT	125	NITE	-J.a	тте	GII	130	GTA	ART	781	HIB	135
App	Leu	TÄN	PTO	Glu	Asn	Leu	Leu	Leu		Sor	Lys	Сув	Σув	
				140	_		_	_	145	_	_	_	_	150
ATE	ALA	val	Lув	Leu 155	Ala	Авр	Phe	Gly		Ala	Ile	Glu	Val	
Glv	Asp	Gla	Gln		Tra	Phe	Glv	2he	160 Ala	alv	Thr	Pra	alv	165 Tvr
				170		•			175				1	180
Fén	ser	Pro	Glu		ren	Arg	ГЛВ	Glu		Tyr	01y	Lyø	₽±Ф	
7. com	T1-	T	n.1	105	۳٦.,	10-1	F1-	1	190	<b>-</b> 1 -	T	7	17- 1	195
мэр	118	Trp	HIM	200	GTÅ	AGIT	FIA	PAI	205	TIE	rea	rea	VAI	210
Tyr	Pro	Pro	Ph≑	Trp	Azp	Glu	Авр	gl <sub>n</sub>		Lys	Lou	Tyr	Gln	
=		_		215					220			-		225
Ila	Lув	Ala	Gly	Ala 230	Tyr	Авр	Phe	Pro		Pro	Glu	Tip	ABP	
val	Thr	Pro	Glu		Lvs	Asn	Leu	Ile	235 Aen	Gln	Met	Leu	Thr	240 Ile
				245	•				250					255
Agn	Fro	Ala	Lys		Ile	Thr	Ala	His		Ala	Leu	Lys	His	
الخدوران	ust	Cye	Gln	260	Sav	⊕h-se	us!	23.0	265	Mon	llot	nia	N source	270
111	101	CYE	GIH	375	367		L-T7	VIE	290	NEL	wer	HIS	мiй	285
Glu	Thr	Val	Olu	Сув	Lou	Lyo	Lys	Phe		Ala	Arg	Arg	Lys	
_				290					295				_	300
тйа	GTA	Ala	IIB	105	Thr	ThT	Ket	Leu	310	Thr	Arg	A211	Phe	Ser
Ala	Ala	Lys	₽♠∺		Leu	Aen	Lyg	Lys		Asp	Gly	Val	Lyp	
				320					325	_	_			330
His	Thr	Asn	Eer		Lya	Asn	Eer	Ala		Ala	Thr	Ser	Pro	_
Glv	Thr	Leu	Pro	335 Pro	Ala	Aža	Zı <b>≞</b> u	glo	340 9ar	9er	don	9er	Bla	345
<b></b> .				350	***	1	778	0.0	355	D-13-2	nep	M 1.54	UVA	360
Thr	Thr	Ile	Glu		Glu	Asp	Ale	Lye		Arg	ГЛВ	Gln	Glu	
<b>T</b> T =		<b>m</b> 1	<b>m</b> .	365	<b>41</b> –	¥	• 7 .	43	370		_	_	245	375
TTB	тйа	Thr	Thr	380	Gin	тел	TTe	GIU	385	Val	ABD	ABI	GIA	ASD 350
Phe	Glu	Ma	Tyr		Lya	Ile	Cys	Azp		Gly	Leu	Thr	Ser	
				395					400					405
Glu	Pro	Glu	Ala		gly	ಗಾತನ	Leu	Val		Gly	Net	Азр	Phe	
Ara	Phe	Tyr	Phe	410 Glu	Aen	Leu	Len	Ala	415 7.ve	2 an	Ser	Isre	Pro	420 Tle
-3		<b>.</b> -		425					430			-,-		435
His	The	Thr	Ile		Asn	Pro	His	Val		٧al	lle	Gly	Olu	_
a i e		Сув	тіл	440 ano	Stitues	TIA	3	T. car	445	O1	Mr. see	T] -	B 0	450
-11 d	LTT CT	—), p	TT ==	455	TÄL	+1 <b>6</b>	ज्यत	пец	460	GTI	TYP	TTG	мар	465
Gln	GLy	Arg	PTC		Thr	Sar	Q1n	Ber		Glu	Thr	Azg	Val	

470 475 His Arg Arg Asp Gly Lys Trp Gln Asn Val His Phe His Cys Ser 485 490 Gly Ala Pro Val Ala Pro Leu Gla

<210> 19 <211> 433 <212> PRT <2135 Homo sapiena

<220> <2215 misc feature

c223> Incyte Clone Number: 1512656

<400> 19 Met Thr Gly Glu Ala Gln Ala Gly Arg Lys Arg Ser Arg Ala Arg Pro Glu Gly The Glu Pro Val Arg Arg Glu Arg The Gln Pro Gly 20 Lou Gly Pro Gly Arg Ala Arg Ala Met Ala Ala Glu Ala Thr Ala val ala Giy Ser Gly Ala Val Gly Gly Cys Leu Ala Lys Asp Gly 50 Lou Gln Gln Ser Lys Cys Pro Asp Thr Thr Pro Lys Arg Arg Arg 70 **6**5 Ala Ser Ser Leu Ser Arg Amp Ala Glu Arg Arg Ala Tyr Gln Trp 80 85 Cy# Arg Glu Tyr Lou Gly Gly Ala Trp Arg Arg Val Gln Pro Glu 95 100 Glu Leu Arg Val Tyr Pro Val Ser Gly Gly Leu Bor Asn Leu Lau 115 110 Pho Arg Cys Ber Leu Pro Asp His Leu Pro Ser Val Gly Glu Glu 125 130 Pro Arq Glu Val Leu Leu Arg Leu Tyr Gly Ala Ils Leu Gln Gly 145 140 Val Asp Ser Leu Val Leu Glu Ser Val Met Phe Ala Ile Leu Ala 160 Glu Arg Ser Led Gly Pro Gln Led Tyr Gly Val Phe Pro Glu Gly 175 170 Arg Lau Glu Gln Tyr Ile Pro Ser Arg Pro Leu Lys Thr Gln Glu 190 185 Leu Arq Glu Pro Val Leu Ser Ala Ala Ile Ala Thr Lye Net Ala 205 200 Glm Phe His Gly Met Glu Met Fro Phe Thr Lys Glu Pro His Trp 215 220 Leu Phe Gly Thr Met Glu Arg Tyr Leu Lye Gln Ile Gln Asp Leu 235 230 Pro Pro Thr Gly Leu Pro Glu Met Asn Leu Leu Glo Met Tyr Ser 250 245 Lou Lys Asp Glu Met Gly Asn Leu Arg Lys Leu Leu Glu Ser Thr 265 Pro Ser Pro Val Val Phe Cys His Asn Asp Ile Gln Glu Gly Asn

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275
                                     280
Ile heu heu heu Ser Glu Pro Glu Asn Ale Asp Ser heu Met heu
Val Amp Phe Glu Tyr Ser Ser Tyr Amn Tyr Arg Gly Phe Amp Ile
Oly Ash His Phe Cys Glu Trp Val Tyr Asp Tyr Thr His Glu Glu
Trp Pro Phe Tyr Lys Ala Arg Pro Thr Asp Tyr Pro Thr Gln Glu
                335
                                     340
                                                         345
Oln Gln Leu His Fhe Ile Arg His Tyr Leu Ala Glu Ala Lys Lys
                350
                                     355
Gly Glu Thr Leu Ser Glu Glu Glu Glu Arg Lys Leu Glu Glu Asp
                365
                                     370
Lou Leu Val Glu Val Ser Arg Tyr Ala Lou Ala Ser His Phe Phe
                380
                                     385
Trp Gly Leu Trp Ser Ile Leu Gln Ala Ser Met Ser Tor Ile Glu
                395
                                     400
Phe Gly Tyr Leu Asp Tyr Ala Gln der Arg Phe Gln Phe Tyr Phe
                410
                                     415
                                                         420
Gln Gin Lys Gly Gln Leu Thr Ser Val His Ser Sor Sor
                425
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<211> 527

<212> PRT

<213> Homo sapiene

<220>

<221> misc\_feature

<223> Incyte Clone Number: 2098635

<400> 20

Met Ser Leo Cys Gly Ala Arg Ala Asa Ala Lys Met Met Ala Ala Tyr Asn Gly Gly Thr Ser Ala Ala Ala Ala Gly Kis Kis His His His His Eis His Leu Pro His Leu Pro Pro Pro His Leu Leu His His His His Pro Gln His His Leu His Pro Gly Ser Ala Ala Ala 50 55 Val His Pro Val Gln Gln His Thr Bor Ser Ala Ala Ala Ala Ala 65 70 Ala Ala Ala Ala Ala Ala Ala Met Leu Asn Pro Gly Gln Gln 2,9 Gim Pro Tyr Phe Pro Ser Pro Ala Pro Gly Gin Ala Pro Gly Pro 95 100 Ala Ala Ala Pro Ala Glo Val Glo Ala Ala Ala Ala Ala Thr LIO 115 Val Lys Ala Ris His His Oln His Ber His His Pro Gla Gla Gla 1.25 130 Leu Asp The Glu Pro Asp Arg Pro The Gly Tyr Gly Ala Phe Gly 140 145 Val Val Trp Ser Val Thr Asp Pro Arg Asp Gly Lys Arg Val Ala 355 160 Leu Lys Lys Met Pro Asn Val Phe Gin Asn Leu Val Ser Cys Lys

				170					175					180
Arm	Val	Phe	Arq		Lau	Lys	Mẹţ	Leu		Phe	ths	Lys	Him	quA
•			-	185					190					195
<b>rr</b> A	val	Leu	Ser	Ala	Leu	Asp	Ile	Leu	Gln	PYC	PTC	His	IJe	
				200			_		205	_			_	210
<b>ፐ</b> ሃ≭	₽h¢	glų.	Ģlų		Tyr	Vel	Vėl	Thr		L≙u	Met	Gin	ser	225
		_	-7 -	215	11- 1	<b>4</b>	<b>5</b> 1	<u>سا</u> ہے	220 Dec	Lan	¢o.	Per	Son	
Leu	H1B	Lya	119	11e	Val	Dar	LLU	PTU	235	Беи	□ <b>€</b> :1	DET	nop	240
3741	Tarm	1741	Ph≠		Tyr	Gln	Ile	Leu		alv	Leu	Lye	Tyr	
1001	٠, ۵			245	-,-				250			-	-	255
His	Ser	Ala	Gly		Leu	Нiв	Arg	Asp	Ile	Lys	PYC	Gly	ABD	Leu
			_	250					255					270
Lau	Val	Aon	Ser	Asn	್ಗಳ	Val	Ι¢μ	Lys		Cyp	Азр	Phe	Jly	Leu
				275				_ 0	280			m \	-1-	285
Ala	Arg	Val	Glu		Leu	Авр	Glu	Ber		819	Met	THY	GII	300
	-, -	<b></b>		290	Tyr		a la	DWA	295	т1 д	Tuein de	N.++	aív	
Val	AgT	TOX	OTD	305	тут	му	итп	FIU	310		4.4	F1'	~~J	315
Arg	wie.	Tur	Ser		Ala	Ils	ABD	Ile		Ser	val	Gly	Сув	
1111 10		-1-		320			_		335			_	_	330
Ph¢	Ala	Glu	Leu	Leu	Gly	Arg	Arg	Ile	rea	Phe	Gln	ala	Gln	
				335					340					345
Pro	Ile	Gln	Gln		Авр	Leu	Ilo	Thr		Leu	Lau	Gly	Chr	Pro
			_ •	350					355		10 1 n	T 250	a 1	360 #10
Ser	Leu	GIU	ATE		Arg	тит	нтч	CAR	370	СΙΎ	'aru	БЪБ	ara	375
<b>T</b> 1 -	Len	To second	. ena	365 Den	His	Term	Gla	Pro		Leu	Рта	VAL	Leu	_
TTG	Der	ur A	GIY	380	*, 20	<b></b> ,	<b>T</b> F.11		385					390
Thr	Leu	Ser	Ser		Ala	Thr	Hie	Glu	Ala	Val	His	Leu	Leu	Сув
				395					40D					405
Arg	Met	Lou	Val	Phe	Азр	Pro	Ş¢r	Lуя			8er	Ala	Lys	Asp
				410					415		•		. m	420
Ala	Lau	. Ala	. Hie			Leu	Asp	GTA	GIY 430		Leu	arg	TAT	Ніэ 435
m			۸	425		Cre	Dh:	Ser			Thr	Glv	Ara	Val
TRE	Cys	i rimt	Cya	440		-, •	- ·		445			~-,	•	450
Tyr	Thr	Ser	Aet			Pro	Val	The	ABI	Pro	ь Гув	Phe	Авр	Asp
_				455	i				460	ı				465
Thr	Pho	Glu	Lys	Aer	Leu	3¢r	9¢r	Val	ATS	(T)	. Val	, Typ	g1u	Ile
				470	l				475	i				490
Ile	Hie	Gli	i Phe			Glu	Gl	ıGlr			ABI	ı Arş	l Man	Pro
_				405			. 711-	. 814	490 . Dh.		· Œ=•	r Dhe	. T14	495 Ser
Leu	Cya	9 []#	e abi	1 PTC 500		, cel		. H.6	509		- Ç <u>.</u>			Ser 510
Rav	• ሞት•	• ນລໄ	וא ו			ĝe?	Glı	ı (Cet		_	s 6es	r Pro	Lei	. Val
201				519				•	520					525
Ten	<b>01</b> 1	ı												

<2115 322

<212> PRT

<213> Homo sapisos

<220>

<321> misc\_feature
<223> Incyte Clone Number: 2446646

<400> 21 Met Glu Gly Ile Ser Asn Phe Lys Thr Pro Ser Lys Leu Ser Glu 10 Lys Lys Lys Ser Val Leu Cys Ser Thr Pro Thr Ile Asn Ile Pro 25 Ala Ser Pro Phe Met Gln Lys Leu Gly Phe Gly Thr Gly Vel Asn Val Tyr Leu Met Lys Arg Ser Pro Arg Gly Leu Ser His Ser Pro 55 Trp Ala Val Lys Lys Ile Asn Pro Ile Cym Asn Asp His Tyr Arg 65 Ser Val Tyr Gln Lye Arg Leu Met Aep Glu Ala Lys Ila Leu Lys 95 Ser Lau Bis His Pro Asn Ile Val Gly Tyr Arg Ala Phe Thr Glu 95 100 Ala Aso Asp Gly Ser Leu Cys Leu Als Met Glu Tyr Gly Glu Glu 110 115 Lys Ser Leu Asn Asp Leu Ila Glu Glu Arg Tyr Lys Ala Ser Gin 125 130 Asp Pro Phe Pro Ala Ala Ile Ile Leu Lys Val Ala Leu Asn Mat 140 145 Ala Arg Gly Leu Lys Tyr Leu Kis Gln Glu Lys Lys Leu Leu Kis 155 160 Gly Asp Ite Lys Ser Ser Asn Val Val Ile Lys Gly Asp 2he Glu 175 The Ile Lys Ile Cys App Vel Gly Val Ser Leu Pro Leu App Glu 185 190 Asn Met Thr Val Thr Asp Pro Glu Ala Cys Tyr Ile Gly Thr Glu Pro Trp Lys Pro Lys Glu Ala Val Glu Glu Asn Gly Val Ile Thr Amp Lys Ala Amp Ile Phe Ala Phe Gly Leu Thr Lou Trp Glu Met Met Thr Leu Sor Ile Pro His Ile Aen Leu Ser Aen Aep Asp Asp 245 250 Amp Glu Amp Lye Thr Pha Amp Glu der Amp Phe Amp Amp Glu Ala 250 265 Tyr Tyr Ala Ala Lea Gly Thr Arg Pro Pro Ile Asn Mat Glu Glu 275 290 Leu Asp Glu Ser Tyr Glu Lys Val Ile Glu Leu Fhe Ser Val Cys 290 295 Thr Asn Glu Asp Pro Lys Asp Arg Pro Scr Ala Ala His Ile Val 315 305 310 Glu Ala Leu Glu Thr Asp Val 320

<210> 22

<211> 802

<212> PRT

<213> Nomo sapiena

<220>

-221> misc\_feature

<223> Incyte Clone Number: 2764911

<400> 22 Met Glu Glu Glu Gly Gly Ser Ser Gly Gly Ala Ala Gly Thr Ser Ala App Gly Gly Asp Gly Gly Glu Gin Lou Lou Thr Val Lys His 20 Glu Leu Arg Thr Ala Asn Leu Thr Gly His Ala Glu Lys Val Gly 40 Ile Glu Asn Phe Glu Leu Leu Lys Val Leu Gly Thr Gly Ala Tyr 55 Gly Lys Val Phe Leu Val Arg Lys Ile Ser Gly His Asp Thr Gly Lys Leu Tyr Ala Met Lys Val Leu Lys Lys Ala Thr Ils Val Gln Lys Als Lys Thr Thr Glu Nie Thr Arg Thr Glu Arg Gln Val Leu 95 Glu His Ile Arg Gln Ser Pro Pha Leu Val Thr Leu His Tyr Ala 115 110 Phe Gla Thr Glu Thr Lys Leu Rie Leu Ile Leu Asp Tyr Ile Asn 130 125 Oly Gly Clu Lou Phe Thr His Leu Ser Gln Arg Glu Arg Phe Thr 145 140 Glu Hiz Glu Val Gln Ile Tyr Val Gly Glo Ile Val Leu Ala Leu 160 155 Glu His Leu His Lys Leu Gly Ile Ile Tyr Are Ase Ile Lys Leu 175 170 Glu Asm Ile Leu Leu Asp Ber Asm Gly His Val Val Leu Thr Asp 185 190 Phe Gly Leu Ser Lys Glu Phe Val Ala Amp Glu Thr Glu Arg Ala 200 205 Tyr Ser Phe Cys Cly Thr Yle Clu Tyr Met Ala Pro Asp Ile Val 215 220 Arg Gly Gly Asp Ser Gly His Asp Lys Ala Val Asp Trp Trp Ser 235 230 Leu Gly Val Leu Met Tyr Glu Leu Leu Thr Gly Ala Ser Pro Phe 250 245 Thr Vol Aco Gly Glu Lys Acn Sor Glo Ala Glu Ile Ser Arg Arg 265 lle Leu Lys Ser Glu Pro Pro Tyr Pro Gln Glu Met Ser Ala Leu 290 275 Ala Lys Asp Led Ile Gla Arg Led Low Met Lys Asp Pro Lys Lys 295 Arg Leu Gly Cys Gly Pro Arg Asp Ala Asp Glu Ile Lys Glu His 31D 3 D 5 Len Phe Phe Gln Lys Ile Asn Trp Asp Asp Len Ala Ala Lys Lys 325 320 Val Pro Ala Pro Phe Lye Pro Val Ile Arg Asp Glu Leu Asp Val 335 Ser Asn Phe Ala Glu Glu Phe Thr Glu Met Asp Pro Thr Tyr Ser 355 350 Pro Ala Ala Leu Pro Glm Ser Ser Glu Lys Leu Phe Glm Gly Tyr 365 370 Ber Phe Val Ala Pro Ber Ile Leu Phe Lys Arg Asn Ala Ala Val 385 380 Ile Asp Pro Leu Gln Phe His Met Gly Val Glu Arg Pro Gly Val

				395					400					405
Thr	Aen	Val	Ala		Bor	Ala	Met	Ket		qaA	Sex	Pro	Ph≑	
				410					415					420
${ t Gln}$	НŢВ	${ t Tyr}$	Aap	Leu	Азр	Leu	Lув	Авр	Lye	Pro	Leu	Gly	Glu	Gly
				425					430					435
Ber	Phe	8¢r	Ile		AXQ	Lys	CYE	V#1		Lys	Lyp	Ser	AST	
2. T -	The	23-	×z-, 1	440	<b>-1</b> -	<b>-1</b> -	P	T	445	20 - 6-	<b>6</b> 1	T. 7	T	450
wra	PHE	HIS	val	455	TTG	TTA	961.	гув	460	Ner	916	wid	Mail	465
Gln	live	Glu	Ila		Ala	Len	G111	Levi		Gilu.	สาง	Him	Pro	
	-,-			470					475		017			460
Ile	Val	Lув	Leu	жів	Glu	Val	Phe	нів	Asp	Gln	Leu	Hie	Thr	Phe
				495					490					495
Lau	Val	Met	<b>Gl</b> u		Leu	Aun	oly	<b>ው</b> ኒሃ		Ζėμ	Phe	<b>Ģ</b> 1↓	Arg	I1e
_	_	_	_	500	_,	_	-4-3		505	_ •	_			510
ГÀВ	Lys	ГÀВ	Lys		Spe	Ber	Glu	Thr		Ala	BBI	Tyr	Ila	
2 ***	T.aces	T -0-11	Val	515	314	1769	Oav	บสล	520 Mar	TI-Le-	Z ere.	T7.a. 5	រាធិក	525 3741
ALG	TI YE	LIT-U	(ar	530	W+ #	n tra	<b>å</b> Ç.	MT D	535	TIP	WAT.	удд	ЭTУ	54D
Val	His	Arq	Aep		Lve	Pro	Glu	Aan		Leu	₽he	Thr	Aero	
		_	_	545					550				·E	555
neA	Ąsp	Авп	Leu	Glu	Tle	Lys	Ila	Ile	Asp	Phe	Gly	₽hə	Ala	Arg
				560					565					570
Leu	Lyz	Pro	Pro	_	Asn	Gln	$\mathbf{pro}$	Leu	_	Thr	Pro	Сув	Phe	
<b>.</b> .		<b>.</b> .	• • •	575	<b>.</b>		<b>.</b>		58Q		_	~~ ·		585
ren	HTE	тут	Ala	590	Pro	1 <del>3</del> 717	下牵护	,.≑n	595	Gin	APU	GIA	171	600 600
Ġ)n	Sar	CVB	Asp		Tro	Rer	Leu	alv	-	Tla	7.B11	ጥኒ፣ም	Thr	
	0.31	-7-0	3306	605	111	COL	ДСи	Grl	610		200	111	1111	515
Leu	Ser	Gly	Gln		Pro	Phe	Gln	9¢x		Asp	Arg	Ser	Lęц	
				€20					625					630
Сув	Thr	Ser	Ala	Val	Glu	Ile	Met	Lye	Lув	Ile	Lув	Lув	Gly	
	_			635			_	_	540		_			545
Phe	Ser	Ph⊕	Glu		Glu	Ala	ŢΫ́	Lys		Val	Bor	Gln	Glu	
Two	) on	T.em	Ile	€50	clv.	Lau	Len	Thr	655 val	Zor.	Bro.	200	Tarm	660
D) o	, make	пеп	110	665	Gly	пас	пеи	1 111	670	veb	FLO	чеп	шуз	675
Leu	Lys	Met	Ser		Leu	Arg	Tyr	Aen		Tip	Leu	Gln	Aep	
	_			680		_			695	-			_	590
80r	Gln	Leu	ßer	Ser	Asn	Pro	Leu	Mat	$\mathbf{Th}_{\mathbf{L}}$	Pro	Азр	Ilo	Leu	Gly
				695	_		Δ		700					705
Ser	Ser	Gly	Ala		Val	Hie	Thr	Сув		ГÄВ	Ala	Thr	Phe	
<b>*</b> 7 -	nh -		7	710	<b>T</b>	T		<b>6</b> 3	715	~	•	<b>~</b> 1 -	•	720
HIG	FIII	неп	Lys	725	rya	wrd	GLU	GIY	730	cya	Pan	GIM	АВЛ	735
A 650	Lvs	Ala	Pro		Ala	Lva	Àro	Aro		Met	Luce	Lives	Thr	
	4 -			740		-, •	• 11. 3		745	11.5.5	-,	-J-		750
Thir	Ser	Thr	Glu		Arg	Ser	Ser	Ser		Glu	Ser	Ser	Hie	
				755	_				760					765
Ser	9¢r	₽¢¥	Hís		His	Gly	Lyg	Thr		Pro	Thr	Ly≴	Thr	
£17			_	770 -		_	_	_	775	_		_,	_	780
ATU	FID	Ber	ABI		ATA	Авр	Ber	Asn		PTC	GLu	Thr	Len	Phe
G) n	Phe	Ser	Aep	785 6er	Val.	عاج			790					795
				800	F									

<210> 23 <211> 641 <212> PRT <213> Homo sapions

<220>

<2215 misc\_feature

<223> Indyte Clone Number: 3013946

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340

Thr Asn Ser Thr Lys Asn Ser Ala Ala Ala Thr Ser Pro Lys Gly

335

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Thr Leu Pro Pro Ala Ala Leu Glu Pro Gln Thr Thr Val Ila His
                350
                                     355
Ast Pro Val Asp Gly Ile Lys Glu Ser Ser Asp Ser Ala Asn Thr
                                     370
Thr Ile Glu Asp Glu Asp Ala Lys Ala Pro Arg Val Pro Asp Ile
                                     365
Leu Ser Ser Val Arg Arg Gly Ser Gly Ala Pro Glu Ala Glu Gly
                395
                                     400
Pro Leu Pro Cys Pro Ser Pro Ala Pro Pho Gly Pro Leu Pro Ala
                410
                                     415
Pro Ber Pro Arg Ile Ser Asp Ile Leu Asn Ser Val Arg Arg Gly
                                     430
Ser Gly Thr Pro Glu Ala Glu Gly Pro Leu Ser Ala Gly Pro Pro
                440
                                     445
                                                         450
Pro Cys Leu Ser Pro Ala Lou Lou Sly Pro Leu Ser Ser Pro Ser
                 455
                                     450
Pro Arg Ile Ser Asp Ile Leu Asn Ser Val Arg Arg Gly Ser Gly
                 470
                                     475
The Pro Glu Ala Lys Cly Pro Ser Pro Val Gly Pro Pro Pro Cys
                 485
                                     490
                                                         495
Pro Ser Pro Thr Ile Pro Gly Pro Leu Pro Thr Pro Ser Arg Lys
                500
                                     505
Gin Glu Ilo Ilo bys Thr Thr Glu Cin Leo Ile Glu Ala Val Asn
                515
                                     520
Asn Gly Asp Phe Glu Ala Tyr Ala Lys Ile Cys Asp Pro Gly Leu
                530
                                     535
Thr Ser Phe Glu Pro Glu Ala Leu Gly Asn Leu Val Glu Gly Met
                                     550
Amp Pho Ris Arg Pho Tyr Phe Glu Am Leu Leu Ala Lye Am Ser
                                     565
Lye Pro Ile His Thr Thr Ile Leu Asn Pro Ris Val Ris Val Ile
Gly Glu Aap Ala Ala Cys Ile Ala Tyr Ile Arg Leu Thr Gln Tyr
Ile Amp Gly Gln Gly Arg Pro Arg Thr Ber Gln Ber Glu Glu Thr
                                     610
Arg Val Trp His Arg Arg Asp Gly Lys Trp Gln Asn Val His Phe
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                                     625
His Cys Ser Gly Ala Pro Val Ala Pro Lou Gln
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<211> 588

<212> PRT

<213> Homo sapiene

<320 ≥

<221> misc\_feature

<223> Incyte Clone Number: 067967

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Val Tyr Asp Thr Phe Nat Met Ile Asp Glu Thr Lys Cys Pro Pro

				25					40					45
Chra	Art.	Lan	Val	35 Lau	Cva	Asti	Pro	Sor		Pro	Pro	Вех	Pro i	
				50					55					60
Arg	Гел	Aan	Ke⊳		Thr	Glu	Glr.	Phe		Gly	Asp	HTB	Thr	75
- L	nl	7 611	3	55 01:0	alv	Glu	Mah	Large	70 741	Glu	ጠኒክ	Leu	Phe ·	
HTB	FINE	₽≅Æ	жар	90	GLY	GIU	MEC	272	\$5					90
Olu	Pho	Gly	леA		Lyp	9¢r	Arn	The	Ilo	g1n	Sex	ù sp	Oly	11¢
				95					100					105
Ber	ÀВР	Ser	Glu		Суа	Ser	PID	Thr	115	ser	GID	стХ	Lув	120
Ser	) Lon	Chra	ľæ11	110 Asc	Thr	Val	Lwa	Gor		Ser	Ser	Ser	Lys	
				125					13¢					135
Pro	Lys	Val	Val		Leu	Thr	Pro	Glu		Ala	Lệđ	Lye	Gln	Tyr
_			<b>.</b>	140	n.1 -	<b>*</b>	e de la compansión de l	Tare	145	dlu.	Tla	Tla	Aøn	150 Tvr
ГАВ	HJB	หาล	Pen	155	WIN	TÀT	·9111	Trke	150	GIG	11.5			165
Pro	Glu	Ile	<b>ፒ</b> ን'ድ	₽b€	Val	Gly	Pro	Asn	Ala	Γλŧ	Lys	Arg	His	Oly
				170					175					160
Val	Ile	Gly	Gly	Pro 195	Aan	Apn	GIA	GIÅ	Tyr 190	dew	wab	ъта	Asp	195
Ala	Tyr	Ile	жів		Pro	AIG	Авр	Hie		Ala	Tyr	Arg	Tyr	
				200					205					210
Val	Lou	Гуэ	Ile		Gly	Lys	θlγ	Ber		Gly	Glu	Val	Ala	Ary 225
77n l	m	2 an	uda	215 Tara	T.e.ii	Avet	Gln	ጥኒተተ	220 Val	Ala	Leu	Lve	Met	
VAL	туг	жыр	NT 0	230	пец	277.24	011	-,-	235					240
Arg	Asn	Glu	Lye	Arg	Phe	His	Arg	Gln		Ale	Glu	Glu	]le	<b>92.3</b>
				245	_	_	<del>4</del> 71 –		250	The se	<b>⇔</b> 7••	e o e	Wat	255
Ile	Leu	Glu	HIB	260	Lya	ьув	GII	Авр	ъув 265	TIST	GTÅ	Per	Met	270
Val	Ile	Hie	. Met		Glu	Ser	Phe	Thr		Arg	Agn	RTB	Val	Сув
				275					290					285
Not	Ala	Phe	Glu		Leu	Ser	Ila	Авр	ն <b>e</b> ս 295		Glu	Lou	Ile	300 300
1329	APT	. Care	Phe	390 290	Glv	Phe	ger	Val			. Val	Arg	Lys	
_				305					310					315
Ala	Gli	. Bei	: Ile			ser	Leu	Aep			Hia	Lya	Asn	Lye 330
~· 4 -		75'-		330		Tarm	Dyna	. /37.0	325 Nec		. Ta≐s:	. Les	Ly#	
TTG	, TTC	: нц	ғ Фун	444 335		ப்பந்த		, 446	340					345
His	g Gly	Arg	3 Sei	Ser	The	Lye	val	Ile	e Aag	) Phe	e Gly	ser ser	Ser	Сув
			_	350		_			353			. 3320	nks	360
Phe	e Oli	ı Ty:	r Gli	1 Lye 365		ı Tyr	Thi	. TAI	37(		ı aer	- ALL	, Fhe	Tyr 375
Arv	r Ala	ı Pr	o Gli			. Leu	. Gly	/ Bez			Sex	Thi	BEO	Ile
				380	•				359	5				390
Anj	, Il	+ Tr	p ₽¢:			Cye	ılle	F Ter	ואו	5 Gl1	ı Lei	ı Let	1 Thr	Gly 405
e41.	- 5-		n Dh	395 - Tro		ر د هار	ו אַר	s dla	401 دای د		o Glo	ı Lası	ı Ala	Суз
				41{	)				41	5				420
Mei	t Ne	<b>B</b> 1	u Lei			y Niel	- Pro	a Psy			a Le	ı Lei	ı Əlu	: Bln
_			_ =	425			_ 443		43		o (41)	<sub>ም</sub> ዋን፣	<b>P</b> FF	435 Arc
Вe	r Ly	э Ar	g Al	a Lya 441		ימא	a TT,	e 248)	n 68 44	ւ Իչ	- AT	,		Arg 450
Tv	r Çv	<b>#</b> 9¢	r Va	1 Th	r Th	r Gl	n Al	a A8			g Va	l Va	l Leu	yal
-	-													

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455
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Giy Gly Arg Ser Arg Arg Gly Lys Lys Arg Gly Pro Pro Gly Ser
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Lys Asp Trp Gly Thr Ala Leo Lys Gly Cys Asp Asp Tyr Leu Phe
The Glu Phe Leu Lys Arg Cys Leu His Trp Asp Pro Sor Ala Arg
                500
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Lau Thr Pro Ala Gln Ala Leu Arg His Pro Trp Ile Ser Lys Ser
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Val Pro Arg Pro Leu Thr Thr Ile Asp Lys Val Ser Gly Lys Arg
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Val Val Asn Pro Ala Ser Ala Phe Gin Gly Leu Gly Ser Lys Leu
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                                     550
Pro Pro Val Val Gly Ile Ala Asn Lys Leu Lys Ala Asn Lou Met
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<211> 389

<212> PRT

<213> Homo sapiens

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<2215 misc feature

<223> Incyte Clone Number: 346275

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Ber Asp Phe Gly Leu Ser Lys Met Glu Gly Lys Gly Asp Val Met 205 Ser Thr Ala Cys Gly Thr Pro Gly Tyr Val Ala Pro Glu Val Lou 220 215 Ala Gln Lye Pro Tyr Ser Lys Ala Val Aep Cys Trp Ser Ile Gly 235 230 Val Ile Ala Tyr Ile Leu Leu Cys Gly Tyr Pro Pro Phe Tyr Asp 250 245 Glu Asn Asp Ser Lys Lou Phe Glu Gln Ile Lou Lys Ala Glu Tyr 265 Glu Phe Amp Ser Pro Tyr Trp Amp Amp Ile Ser Amp Ser Ala Lym 285 275 Amp Pha lle Arg Amn Lou Met Glu Lym Amp Pro Amn Lym Arg Tyr 295 290 Thr Cys Glu Gln Ala Ale Arg His Pro Trp He Ala Gly Asp Thr 310 Ala Leu Asn Lys Asn Ile Kis Glu Ser Val Ser Ala Gln Ile Arg 325 330 Lys Asn Phe Ala Lys Ser Lys Trp Arg Gln Ala Phe Asa Ala Thr 340 335 Ala Val Val Arg Hie Met Arg Lys Leu His Leu Gly Ber Ber Leu 355 350 Asp Ser Ser Asn Ala Ser Val Ser Ser Ser Leu Ser Leu Ala Ser **370** 365 Gln Lys Amp Cys Ala Tyr Val Ala Lym Pro Glu Ber Leu Ser 385 380

<210> 26 <211> 343 <212> PRT <213> Homo sapiena

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Cya Ser Phe Leu Asp Asp Leu Leu Glu Leu Arg Asp Glu Glu beu
                140
                                     145
Ser Lys Glu Ser Glo Glu Thr Ash Trp Phe Ser Als Pro Ser Als
Leu Arg Val Tyr Gly Gln Tyr Leu Aen Leu Asp Lys Asp His Asn
                170
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Gly Met Lou Ser Lys Glu Glu Leu Ser Arg Tyr Gly Thr Ala Thr
                185
                                     190
Met Thr Aen Val Phe Leu Asp Arg Val Phe Gln Glu Cys Leu Thr
                200
                                     205
Tyr Asp Gly Glu Not Asp Tyr Lys Thr Tyr Leu Asp Phe Val Leu
                215
                                     220
Ala Leu Glu Asn Arg Lys Glu Pro Ala Ala Leu Gln Tyr Ile Pho
                                     335
                230
Lys Leu Leu Asp Ile Glu Aon Lys Gly Tyr Leu Aon Val Phe Ser
                                     250
                245
Leu Asn Tyr Phe Phe Arg Ala Ile Gln Glu Leu Met Lys Ile His
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                                     255
Gly Gln Asp Pro Val Ser Phe Gln Asp Val Lys Asp Glu Ile Phe
                275
                                     280
Asp Met Val Lye Pro Lys Asp Pro Leu Lys Ile Ser Leu Gln Asp
                290
                                     295
Lou Ile Asn Ser Asn Gln Gly App Thr Val Thr Thr Ile Leu Ile
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Asp Leu Asn Gly Phe Trp Thr Tyr Glu Asn Arg Glo Ala Leu Val
                                     325
Ala Asn Asp Ser Clu Asn Ser Ala Asp Leu Asp Asp Thr
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<310> 27

<211> 184

<212> PRT

<213> Home sepiens

<220>

<221> misc feature

<223> Incyte Clone Number: 2696537

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Gly Arg Ser Cys Ala Asn Pro Asn Val Gly Phe Gln Arg Gln Leu
125 130 130 135

Gln Glu Phe Glu Lys His Glu Val His Gln Tyr Arg Gln Trp Leu
140 145 155

Lys Glu Glu Tyr Gly Glu Ser Pro Leu Gln Asp Ala Glu Glu Ala
155 160 165

Lys Asn Ile Leu Ala Ala Pro Gly Ile Leu Lys Phe Trp Ala Phe
170 175 180

Leu Arg Arg Leu

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<2235 Incyte Clone Number: 2054049

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 Leu Arg Lys Leu Lys Glu Ile Val Tyr Pro Asn Ile Glu Glu Thr
 His Trp Lau Ser Asn Lau Glu Ser Thr His Trp Lau Glu His Tle
                                      100
 Lys Leu Ilo Leu Alz Gly Ala Leu Arg Ile Ala Asp Lys Val Glu
                                      115
 Ser Gly Lys Thr Ser Val Val Val His Cyr Ser App Gly Trp Asp
                                      130
 Arg Thr Ala Gin Leu Thr Ser Leu Ala Met Leu Met Leu Asp Gly
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                                     145
 Tyr Tyr Arg Thm ile Arg Cly Phe Glu Val Leu Val Glu Lys Glu
                 155
                                     160
 Trp Leu Ser Phe Gly His Arg Phe Glo Leu Arg Val Gly His Gly
                 170
                                     175
 Asp Lys Asn Kis Ala Asp Ala Asp Arg Ser Pro Val Phe Leu Gln
                                     190
Pha Ile Asp Cya Val Trp Gln Met Thr Arg Gln Phe Pro Thr Ala
                 200
                                     205
Phe Glu Phe Asn Glu Tyr Phe Leu Ile Thr Ile Leu Asp Ris Leu
                 215
                                     220
Tyr Ser Cys Leu Pha Gly Thr bhe Leu Cys Azn Ser Glu Gln Gin
                 230
                                     235
Arg Gly Lys Glu Asn Lew Pro Lys Arg Thr Val Ser Lou Trp Sor
                 245
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Tyr lle Agn Ser Gln Leu Glu Asp Phe Thr Agn Pro Leu Tyr Gly
                260
Ser Tyr Ser Asn His Val Leu Tyr Pro Val Ala Ser Met Arg His
                                                         270
                275
                                     280
Lou Glu Leu Trp Val Gly Tyr Tyr Ile Arg Trp Asn Pro Arg Met
                290
Lys Pro Gln Glu Pro Ile His Asn Arg Tyr Lys Glu Leu Leu Ala
                                     310
Lys Arg Ala Glu Leu Gln Lys Lys Val Glu Glu Leu Gln Arg Glu
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The Ser Asn Arg Ser Thr Ser Ser Ser Shu Arg Ala Ser Ser Pro
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Ala Gln Cys Val Thr Pro Val Gln Thr Val Val
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<3135 Homo sapiens

<320>

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Gly	qe <i>A</i>	Leu	Leu	Ala 50	Thr	Gly	qeA	Lye	G1y SS	Ģ1y	Arg	Val	Val	Ile 60
Phe	@1n	¥አā	Glu	91n 65	<b>31</b> u	Asn	Lys	Ser	A27g 70	FTO	Hje	8er	Arg	Gly 75
Glu	Tyr	IBA	val	Tyr 80	Ber	rdT	Phe	Gln	Ser 85	нів	Glu	Pro	Glu	Phe 90
Asp	Tyr	Leu	Lys	95 9 <del>ex</del>	Leu	<b>3</b> 14	Ilę	<b>01</b> u	<b>0l</b> u 100	Lys	Ils	Apn	Lys	Ile 105
Arg	Trp	Leu	Pro	Gln 110	Gln	ABN	Ala	Ala	Hie 115	Phe	L€u	Leu	Ser	Thr 120
ana	Asp	Lys	Thr	Ila 125	Lye	Leu	Trp	Lys	Ila 130	ßer	Ġlu	Arg	Авр	lys 135
Arg	Ala	Glu	Gly	TYY 140	Aen	Leu	Lye	Авр	91u 145	Aep	gly	yrg	Leu	Arg 150
Asp	<b>ेप</b> री	Phe	Arg	Ile 155	Thr	Ala	ren	Arg	Val 160	Pro	Ile	Leu	Lys	Pro 165
Met	Asp	Leu	Met	Val 170	Glu	BĽA	Ser	Pro	Arg 175	Arg	Il≑	Ph¢	Ala	Asn 190
		Thr	-	185					190					195
		TYY		200					205					210
		Ils		315					220					225
		Met		230					235					240
		Ris		245					250					255
		Arg		260					265					270
		Lye		275					280					285
		ßer		290					395					300
		G1y	-	305					310					315
		Aep		320					325					320
				335					360					ABI 345
_				350					355					Авр 360
				365					370					275
_		_		380					385					390
				395	i				400					The 405
				410	1				415	i				120
				425	i				430	ı				435
Val	Ile	Als	. Val	. Ale	Ale	Thr	Aen:	) Aer	i Leu	L Tyri	116	± 1116	: FITT	Aap

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44 ü
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$¢$yeaeyey eyeyteacey teamytatya ceggegyyay etyemyege gyetyyaeyt 180
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<213> Homo sapiana
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<221> misc\_feature

<223> Incyte Clone Number: 156108

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<220>

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<223> Incyte Chone Number: 2883243

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<220>
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WO 00/06728

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<213> Home sapiens
<220>
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<223> Incyte Close Number: 5116906
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<213> Homo eapiens
<230>
<221> misc_feature
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Cagaaatttg ggaaascotg cottatasca staassgtgs catctggtcc ttgggttgc: 600
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<211> 1023
<212> DNA
<213> Homo sapiens
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<220>
<221> misc feature

<223> Incyte Clone Number: 304421

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acentysace atatogatya gytetyyeee agostottos tyygagatyo ytacycagos 360
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<213> Homo sapiens

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101		Interna	tional Bureau
INTERNATIONAL	APPLICATION PUBLISH	ED L	INDER THE PATENT COOPERATION TREATY (PCT)
(51) International Patent			(11) International Publication Number: WO 00/06728
C12N 15/12, C077 5/10, C07K 16/18	1 1 7 7 7 , C12 1 7/12,	A3	(43) International Publication Date: 10 February 2000 (10.02.00)
(21) International Applica (22) International Filing I			(75) Inventors/Applicants (for US only): HILLMAN, Jennifer, L.
(30) Priority Data: 09/123,494 Not furnished 09/152,814 Not furnished 09/173,482 Not furnished 60/106,889 60/109,093 60/113,796 09/229,005 Not furnished	28 July 1998 (28.07.98) 28 July 1998 (28.07.98) 14 September 1998 (14.09.98) 14 September 1998 (14.09.98) 14 October 1998 (14.10.98) 14 October 1998 (14.10.98) 3 November 1998 (03.11.98) 19 November 1998 (19.11.98) 22 December 1998 (22.12.98) 12 January 1999 (12.01.99) 12 January 1999 (12.01.99)	) ( ) ( ) ( ) ( ) ( ) (	C. [US/US]; 1240 Dale Avenue #30, Mountain View, CA 94040 (US). GUEGLER, Karl, J. [CH/US]; 1048 Oakland Avenue, Menlo Park, CA 94025 (US). BAUGHN, Mariah, R. [US/US]; 14244 Santiago Road, San Leandro, CA 94577 (US). PATTERSON, Chandra [US/US]; 490 Sherwood Way #1, Menlo Park, CA 94025 (US). BANDMAN, Olga [US/US]; 366 Anna Avenue, Mountain View, CA 94043 (US). AU-YOUNG, Janice [US/US]; 1419 Kains Avenue, Berkeley, CA 94709 (US). GORGONE, Gina, A. [US/US]; 1253 Pinecrest Drive, Boulder Creek, CA 95006 (US). YUE, Henry [US/US]; 826 Lois Avenue, Sunnyvale, CA 94087 (US). AZIMZAI, Yalda [US/US]; 2045 Rock Springs Drive, Hayward, CA 94545 (US). REDDY, Roopa [IN/US];
(63) Related by Continuat (CIP) to Earlier A US Filed on US Filed on US Filed on US Filed on	tion (CON) or Continuation-in- Applications  Not furnishe 28 July 1998 (2) 09/123,49 28 July 1998 (2) 09/152,81 14 September 1998 (1)	ed (CI 8.07.9 94 (CI 8.07.9 14 (CI 4.09.9	1081 Tanland Drive, Palo Alto, CA 94303 (US).  P) (74) Agents: BILLINGS, Lucy, J. et al.; Incyte Pharmaceuticals, Inc., 3174 Porter Drive, Palo Alto, CA 94304 (US).

Not furnished (CIP)

Not furnished (CIP)

09/173,482 (CIP)

60/106,889 (CIP)

60/109,093 (CIP)

60/113,796 (CIP)

09/229,005 (CIP)

14 September 1998 (14.09.98)

14 October 1998 (14.10.98)

14 October 1998 (14.10.98)

3 November 1998 (03.11.98)

19 November 1998 (19.11.98)

22 December 1998 (22.12.98)

12 January 1999 (12.01.99) Not furnished (CIP)

12 January 1999 (12.01.99)

- (81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

#### Published

With international search report.

(88) Date of publication of the international search report:

4 May 2000 (04.05.00)

- (71) Applicant (for all designated States except US): INCYTE PHARMACEUTICALS, INC. [US/US]; 3174 Poner Drive, Palo Alto, CA 94304 (US).
- (54) Title: PHOSPHORYLATION EFFECTORS

#### (57) Abstract

US

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Filed on

The invention provides human phosphorylation effectors (PHSP) and polynucleotides which identify and encode PHSP. The invention also provides expression vectors, host cells, antibodies, agonists, and antagonists. The invention also provides methods for diagnosing, treating, or preventing disorders associated with expression of PHSP.

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# INTERNATIONAL SEARCH REPORT

Interr nat Application No

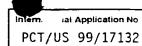
PCT/US 99/17132 a. classification of subject matter IPC 7 C12N15/12 C07K14/47 C12N5/10 C07K16/18 C12N9/12 A61K38/17 According to International Patent Classification (IPC) or to both national classification and IPC B. FIELDS SEARCHED Minimum documentation searched (classification system followed by classification symbols) IPC 7 C07K C12N Electronic data base consulted during the international search (name of data base and, where practical, search terms used) C. DOCUMENTS CONSIDERED TO BE RELEVANT Category of Citation of document, with Indication, where appropriate, of the relevant passages Relevant to claim No. HILLIER, L., ET AL.: "WashU-NCI human EST Χ 5,6,10, project" EMBL SEQUENCE DATA LIBRARY, 6 February 1998 (1998-02-06), XP002121148 heidelberg, germany accession no. AA780791 ISHIKAWA, K., ET AL.: "prediction of the 1-5,9,10Χ coding sequences of unidentified human genes. X. The complete sequences of 100 new cDNA clones from brain which can code for large proteins in vitro" DNA RESEARCH, vol. 5, no. 3, 30 June 1998 (1998-06-30), pages 169-176, XP002121149 the whole document -/--Further documents are listed in the continuation of box C. Patent family members are listed in annex. Special categories of cited documents: \*T\* later document published after the international filing date or priority date and not in conflict with the application but "A" document defining the general state of the lart which is not considered to be of particular relevance. oited to understand the principle or theory underlying the "E" earlier document but published on or after the international "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to "L" document which may throw doubts on priority claim(s) or involve an inventive step when the document is taken alone which is cited to establish the publication date of another document of particular relevance; the claimed invention citation or other special reason (as specified) cannot be considered to involve an inventive step when the document is combined with one or more other such docu-"O" document referring to an oral disclosure, use, exhibition or ments, such combination being obvious to a person skilled in the art. \*P\* document published prior to the international filing date but "&" document member of the same patent family later than the priority date claimed Date of the actual completion of the international search Date of mailing of the international search report 17, 02, 00 9 November 1999 Authorized officer Name and mailing address of the ISA European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo ni,

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	ation) DOCUMENTS CONSIDERED TO BE RELEVANT	
Category <sup>a</sup>	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 98 11234 A (HAWKINS PHILLIP R ;INCYTE PHARMA INC (US); AU YOUNG JANICE (US); G) 19 March 1998 (1998-03-19) the whole document	1-19
Α .	WO 97 02347 A (INCYTE PHARMA INC) 23 January 1997 (1997-01-23) the whole document	1-19
A	WALDEN, P.D. AND COWAN, N.J.: "a novel 205-kilodalton testis-specific serine/threonine protein kinase associated with microtubules of the spermatid manchette"  MOLECULAR AND CELLULAR BIOLOGY, vol. 13, 1993, pages 7625-7635, XP002121150 the whole document	1-19
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Inte. .ational application No

# INTERNATIONAL SEARCH REPORT

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Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)
This international Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons
Claims Nos because they relate to subject matter not required to be searched by this Authomy, namely  Remark: Although claim 19  is directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. X Claims Nos 17, 18, 20 because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful international Search can be carried out, specifically  See FURTHER INFORMATION sheet PCT/ISA/210
3. Claims Nos because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).
Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)
This international Searching Authority found multiple inventions in this international accircation, as follows
As all required additional search fees were timely paid by the applicant, this international Search Report covers all searchable claims.
2. As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos
No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims. Nos.  1-20 partially
Remark on Protest  The additional search fees were accompanied by the applicant's protest.  No protest accompanied the payment of additional search fees

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#### FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

1. Claims: 1-20 partially

Polynucleotide and polypeptide sequences that show homology to Protein Kinases; especially SEQIDs 1,12 and 32,43; the recombinant expression of the same and uses thereof.

2. Claims: 1-20 partially

Polynucleotide and polypeptide sequences that show homology to PKC-potentiated inhibitory protein of PP1; especially SEQIDs 2 and 33; the recombinant expression of the same and uses thereof.

3. Claims: 1-20 partially

Polynucleotide and polypeptide sequences that show homology to STE20-like Protein Kinases; especially SEQIDs 3 and 34; the recombinant expression of the same and uses thereof.

4. Claims: 1-20 partially

Polynucleotide and polypeptide sequences that show homology to Phosphofructokinases; especially SEQIDs 4 and 35; the recombinant expression of the same and uses thereof.

5. Claims: 1-20 partially

Polynucleotide and polypeptide sequences that show homology to Serin/Threonine Protein Kinases; especially SEQIDs 5,6,10 and 36.37,41; the recombinant expression of the same and uses thereof.

6. Claims: 1-20 partially

Polynucleotide and polypeptide sequences that show homology to Phosphatidylinositol-3-kinases; especially SEQIDs 7 and 38; the recombinant expression of the same and uses thereof.

7. Claims: 1-20 partially

Polynucleotide and polypeptide sequences that show homology to Tyrosine or Tyrosine/serine Protein Kinases; especially SEQIDs 8,13,21 and 39,44,52; the recombinant expression of the same and uses thereof.

8. Claims: 1-20 partially

Polynucleotide and polypeptide sequences that show homology

### FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

to Calcium /Calmodulin dependent Protein Kinases; especially SEQIDs 9.18,23.25 and 40,49,54,56; the recombinant expression of the same and uses thereof.

9. Claims: 1-20 partially

Polynucleotide and polypeptide sequences that show homology to Tyrosine Phosphatases or Dual specificity phosphatases; especially SEQIDs 11,29,30 and 42,60,61; the recombinant expression of the same and uses thereof.

10. Claims: 1-20 partially

Polynucleotide and polypeptide sequences that show homology to PEST phosphatase interacting protein; especially SEQIDs 14 and 45; the recombinant expression of the same and uses thereof.

11. Claims: 1-20 partially

Polynucleotide and polypeptide sequences that show homology to SH3-binding proteins; especially SEQIDs 15 and 46; the recombinant expression of the same and uses thereof.

12. Claims: 1-20 partially

Polynucleotide and polypeptide sequences that show homology to NIK-kinases; especially SEQIDs 16 and 47; the recombinant expression of the same and uses thereof.

13. Claims: 1-20 partially

Polynucleotide and polypeptide sequences that show homology to Inferferon-induced PK regulators; especially SEQIDs 17 and 48; the recombinant expression of the same and uses thereof.

14. Claims: 1-20 partially

Polynucleotide and polypeptide sequences that show homology to Choline-kinases; especially SEQIDs 19 and 50; the recombinant expression of the same and uses thereof.

15. Claims: 1-20 partially

Polynucleotide and polypeptide sequences that show homology to MAP-related Protein kinases; especially SEQIDs 20 and 51; the recombinant expression of the same and uses thereof.

# FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

16. Claims: 1-20 partially

Polynucleotide and polypeptide sequences that show homology to Ribosomal S6 Protein kinases; especially SEQIDs 22 and 53; the recombinant expression of the same and uses thereof.

17. Claims: 1-20 partially

Polynucleotide and polypeptide sequences that show homology to Protein kinases Dyrk2; especially SEQIDs 24 and 55; the recombinant expression of the same and uses thereof.

18. Claims: 1-20 partially

Polynucleotide and polypeptide sequences that show homology to Protein Phosphatases 2A; especially SEQIDs 26,28,31 and 57,59,62; the recombinant expression of the same and uses thereof.

19. Claims: 1-20 partially

Polynucleotide and polypeptide sequences that show homology to MAP-kinase Phosphatases; especially SEQIDs 27 and 58; the recombinant expression of the same and uses thereof.

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# FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Glaims Nos.: 17,18,20

Claims 17,18 and in part 20 refer to an antagonist and agonist of the polypeptides without giving a true technical characterization. Moreover, no such compounds are defined in the application. In consequence, the scope of said claims is ambiguous and vague, and their subject-matter is not sufficiently disclosed and supported (Art. 5 and 6 PCT). No search can be carried out for such purely speculative claims whose wording is, in fact, a mere recitation of the reults to be achieved.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

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mormation on patent family members

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